1 ABOUT NIH

Biennial Report of the Director

National Institutes of Health

Fiscal Years 2008 & 2009

Volume I

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An electronic version of this report is available at: http://biennialreport.nih.gov and contains many live links to NIH programs, plans, and publications.

Preface

This is the second NIH Biennial Report submitted under the requirement established by Section 104 of the NIH Reform Act (Pub. L. No. 109-482). Appendix A provides the language in the Reform Act that is relevant to this report, along with the language of two subsequent laws that supplement the provisions of the Reform Act—the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85) and the Newborn Screening Saves Lives Act of 2007 (Pub. L. No. 110-204).

NIH hopes that the information in this report serves as a useful reference for understanding NIH activities and operations and welcomes feedback on the report. Did you find the information you were looking for in the report? Was the information useful? What didn't you find that you were looking for? How can the report be enhanced to improve NIH transparency and accountability?

Chapter Organization

Chapter 1 opens with a statement from the Director, NIH, providing an assessment of the state of biomedical and behavioral research. It then provides a description of NIH structure, policies, and procedures focusing on the operations of the extramural and intramural research programs, mechanisms for strategic planning (including the activities and processes of the Division of Program Coordination, Planning and Strategic Initiatives, and its management of the Common Fund), and various cross-cutting activities not covered in the chapters that follow, such as NIH implementation of the American Recovery and Reinvestment Act of 2009, programs that provide the platform for discovery, endeavors to improve research management (such as the effort to enhance peer review), activities to capitalize on discovery, and ways NIH is ensuring responsible conduct of research.

Chapter 2 addresses NIH research activities from the perspective of diseases, disorders, and adverse health conditions. The topics covered include:

- Cancer
- Neuroscience and Disorders of the Nervous System
- Infectious Diseases and Biodefense
- Autoimmune Diseases
- Chronic Diseases and Organ Systems
- Life Stages, Human Development, and Rehabilitation
- Minority Health and Health Disparities

These topics, all categories specified in the NIH Reform Act of 2006 (see Appendix A), are grouped together in one chapter to address the intent of the statute, in terms of presenting information on diseases, disorders, and adverse health conditions in a standardized format. Each topic is addressed in a separate section. The material in each section is organized as follows:

A brief introduction describes and defines the disease or condition, indicates the scope of NIH research activity, provides data on disease burden and related health statistics, and, when available, presents aggregate data on NIH funding for research on the disease or condition. Now that the NIH Research, Condition, and Disease Categories (RCDC) system is in place, for categories on which NIH collects agency-wide funding data, in the electronic version of the report, we provide a live link to detailed project listings. NIH expects to expand the capacity of RCDC in future years, and this will increase the number of Biennial Report categories for which NIH has aggregate agency-wide funding data and project listings.

This introduction is followed by a summary of NIH activity that reflects the breadth and depth of the research and related efforts of Institutes and Centers (ICs) and Office of the Director (OD) program offices whose missions encompass the diseases and conditions addressed in the section.

The summary is followed by notable examples of research activities, such as key programs, initiatives, studies, and accomplishments. The notable examples provide snapshots and highlights of research and related activities and, in so doing, provide further details on many of the activities addressed in the summary as well as details about other activities.

Following the notable examples is a list of strategic plans relevant to the disease/condition. These plans are listed by IC and OD program office, with plans most closely aligned to the topic listed first. Whenever possible, links are provided to websites where additional information is available.

Many ICs and OD program offices have research plans and agendas that, although not specific enough to a topic to be listed in Chapter 2, nonetheless are worth noting because the plans crosscut and underpin NIH activities specific to diseases, disorders, and adverse health conditions. Such plans include those of the Center for Scientific Review, National Institute of General Medical Sciences, National Institute of Environmental Health Sciences, National Human Genome Research Institute, National Institute of Biomedical Imaging and Bioengineering, National Center for Research Resources, National Library of Medicine, NIH Clinical Center, Office of AIDS Research, Office of Behavioral and Social Sciences Research, and Office of Research on Women's Health.

Chapter 2 concludes with a table on NIH funding. The funding information is based on the standard table of NIH Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC), which presents information NIH routinely collects on agency-wide funding in areas of special interest.

Chapter 3 addresses NIH research activities from the perspective of key research approaches and resources. The topics covered include:

Fields and Approaches

- Epidemiological and Longitudinal Studies
- Genomics
- Molecular Biology and Basic Sciences
- Clinical and Translational Research

Tools and Training

- Disease Registries, Databases, and Biomedical Information Systems
- Technology Development
- Research Training and Career Development

Health Information and Communication

- Health Communication and Information Campaigns and Clearinghouses

These topics are all categories specified in the NIH Reform Act (see Appendix A).

NIH research spans many disciplines and every stage of inquiry. Those addressed in this report are of particular interest, based on their citation in the statute. Epidemiological and longitudinal studies examine the causes, courses, and outcomes of health and disease at the population level. Genomic research studies an organism's entire genome (the complete assembly of its genes), focusing on the genome as an interrelated network. Molecular biology and the basic sciences are providing insights into human health and disease at the most fundamental levels, providing information essential to understanding basic human biology and behavior in their normal and diseased states. Through investments in clinical and translational research, NIH is moving basic discoveries into effective treatment and prevention strategies as well as uncovering knowledge gaps that require more basic inquiry.

Similarly, research-enabling activities, such as design, implementation, and maintenance of information systems, the development of new technology, and the training and career development of scientists, provide efficient collection, storage, and access to critical biomedical and behavioral information; generate the tools, tests, devices, and methods that foster new fields of science and medicine; and prepare and hone the minds that propel discovery. The activities in each of these areas extend the capacity of the national biomedical and behavioral research enterprise in critical ways.

Ensuring the uptake of research results by clinical practitioners and the public is another important facet of NIH's mission. Targeted health communication plans and information campaigns that provide science-based information are essential to improving people's health and saving lives.

The material on each of these topics is organized as follows: A brief introduction describes and defines the approach or resource and indicates the scope of NIH research activity. This introduction is followed by a summary of NIH activity that reflects the breadth and depth of the research and related efforts of ICs and OD program offices whose missions encompass the topic area. The summary is followed by notable examples of research activities, such as significant programs, initiatives, studies, and accomplishments. The notable examples provide snapshots and highlights of research and related activities and, in so doing, illustrate the depth and breadth of NIH efforts. In the electronic version of the document, whenever possible, **links** are provided to websites where additional information can be found.

The topic sections in Chapters 2 and 3 each provide an overview and highlights; they are representative rather than comprehensive.

Chapter 4 addresses certain NIH Centers of Excellence. Overall, NIH Centers of Excellence are diverse in focus, scope, and origin. The NIH Centers of Excellence described in this report are a subset—those established by statutory mandate. This chapter provides overviews, progress reports for the FY 2008 and 2009 biennial period (covering programmatic and research activities and outcomes), recommendations, evaluation plans, and future directions for the six congressionally mandated NIH Centers of Excellence programs, which are described in the order of their establishment:

- Alzheimer's Disease Centers (1984)
- Claude D. Pepper Older Americans Independence Centers of Excellence (1989)
- Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (2001)
- National Center on Minority Health and Health Disparities Centers of Excellence (2001)
- Rare Diseases Clinical Research Network (2003)
- New Autism Centers of Excellence (2006), which merged the previously existing Collaborative Programs of Excellence in Autism and Studies to Advance Autism Research and Treatment

Tables listing the centers funded under each mandated Centers of Excellence program appear at the end of the narrative on each program.

The Appendices present reference documents and supporting data. Appendix A provides a copy of the sections of the NIH Reform Act of 2006 (Pub. L. No. 109-482) that require this Biennial Report, as well as the relevant text from two subsequent laws that supplement the provisions of the Reform Act—the Food and Drug Administration Amendments Act

of 2007 (Pub. L. No. 110-85) and the Newborn Screening Saves Lives Act of 2007 (Pub. L. No. 110-204). Appendix B lists and briefly describes the missions of the NIH ICs and the OD program offices. It also supplies links to IC and OD program office strategic plans. Appendix C supplies a copy of the *Common Fund Strategic Planning Report, FY 2009*. Appendix D provides excerpts of *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*, in order to identify clinical research study populations by demographic variables, as is required by the Reform Act. Appendix E consists of data on the primary NIH research training program, the National Research Service Award program, the National Library of Medicine training programs, and NIH graduate medical education activities. Appendix F provides excerpts of the *Report of the Advisory Committee on Research on Women's Health*, in order to include, by reference, that Biennial Report, within this one, as required by Section 486(d)(5) and Section 403 of the Public Health Service Act, 42 U.S.C. 283, which predate the reporting requirement established by the NIH Reform Act of 2006.

Volume I Contents

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Statement of the Director

It is my privilege to present to Congress the Biennial Report of the Director of the National Institutes of Health (NIH) for Fiscal Years (FYs) 2008 and 2009. Thanks to ongoing congressional support, NIH continues the pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability. Indeed, the contributions of NIH to improved health are countless and have touched the lives of not only all Americans, but also of millions of people around the world.

Unique Resources and Opportunities

It is an extraordinary time to be chosen to direct the world's largest biomedical research enterprise. The power of the molecular approach to health and disease has steadily gained momentum over the past several decades, and is now poised to catalyze a true revolution in medicine—ultimately with profound consequences for diagnosis, prevention, and treatment of virtually all diseases. The success of the Human Genome Project and several other major projects that followed quickly afterward have provided a powerful foundation for a new level of understanding of human biology, and have opened a new window into the causes of disease. That includes the revelation of hundreds of previously unknown risk factors for cancer, diabetes, heart disease, hypertension, and a long list of other common illnesses. In the area of cancer, a new ability to achieve comprehensive understanding of the mechanisms responsible for malignancy has already provided insights into diagnostics and pointed to a whole new array of drug targets. Advances in stem cell research—now poised to move forward at an accelerated pace after the President's signing in March 2009 of Executive Order 13505: *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells*—hold great promise for applications to diseases such as Parkinson's disease, type 1 diabetes, and spinal cord injury. New partnerships between academia and industry promise to revitalize the flagging drug development pipeline. An era of personalized medicine is emerging where prevention, diagnosis, and treatment of disease can be individualized, instead of using the one-size-fits-all approach that all too often falls short. Vigorous U.S. support of biomedical research in all these areas promises to save lives, reduce the burden of chronic illness, stimulate the economy, empower new and more effective prevention strategies, and reduce health care costs.

NIH Research Works!

Over the years, NIH research has contributed enormously to the remarkable increase in health and life expectancy in the United States. For example, we have gained 7.4 years of life expectancy from 1961 to 2004. Infant mortality has decreased from 26 deaths per 1,000 live births in 1960 to 6.9 in 2005. Two decades ago, the 5-year survival rate for women diagnosed with breast cancer was 84.3 percent and the annual mortality rate was 32.2 per 100,000. Due in large part to NIH research, the 5-year survival rate has risen to more than 90 percent. Breast-conserving surgery followed by local radiation therapy has replaced mastectomy as the preferred surgical treatment. New non-surgical therapies include combination chemotherapies, hormonal treatments, and new monoclonal antibodies.

In the 1990s, the discovery and development of antiretroviral drugs transformed HIV infection for many infected individuals from a death sentence into a chronic disease. Recently, researchers found that beginning antiretroviral therapy early in children infected with HIV significantly improves their immune systems. Because of this evidence, the HHS Panel on Pediatric Antiretroviral Therapy and Management Guidelines has modified recommendations on when to start HIV antiviral treatment in children.

Just a few decades ago, 30 percent of patients died within 25 years of a diagnosis of type 1 diabetes. One in four diabetics developed kidney failure, and diabetic retinopathy was responsible for 12 percent of new cases of adult blindness. The concept of controlling blood sugar tightly to prevent diabetes-related eye disease, nerve damage, and kidney failure was untested. In 1989, enrollment of 1,441 people with type 1 diabetes was completed in the landmark Diabetes Control and Complications Trial (DCCT). The trial showed that intensive blood sugar control reduced risk for eye, kidney, and nerve

complications by 50 to 75 percent. Upon completion of the DCCT, intensive therapy rapidly became the standard of care nationwide. Nearly all DCCT participants continue to be followed in an ongoing successor study. Now, based on new results from this pivotal study, we see not only continued dramatic reductions in eye, kidney, and nerve complications, but also that heart disease and stroke are cut by more than 50 percent. We also see improved long-term health outcomes: 30 years after their initial diagnosis, fewer than 1 percent of the intensively controlled DCCT participants have become blind, required kidney replacement, or had an amputation. Thus, people with type 1 diabetes are living longer, healthier lives than ever before, largely due to long-term NIH-supported research.

Importantly, as the Nation is in the midst of debating ways to reduce increasing health care costs dramatically, NIH research has resulted in remarkable U.S. gains in health and longevity, often with surprisingly modest investments and often accompanied by significant cost savings. A recent analysis of the trajectory of U.S. population health[1] shows substantial correlation of NIH funding with improved life expectancy, reduced disability rates, and economic benefits. For example, deaths from coronary heart disease have declined by 63 percent in the last 30 years, thanks to a host of new insights about prevention and treatment. These dramatic advances have come about with an investment of just $3.70 per American per year in NIH research support. Another example of savings we have seen over time is the development of a vaccine against *Haemophilus influenzae* type b (Hib), which has resulted in a 99 percent decline in the incidence of this leading cause of bacterial meningitis in children under age 5. This has achieved an estimated medical cost savings of $950 million per year, as well as another $1.14 billion per year in avoidance of lost earnings due to disability of the patient and uncompensated caregivers.[2]

ARRA: Jumpstarting a New Era

It was because of this remarkable synergy between the health and economic impacts of NIH-supported research that Congress directed an extraordinary $10.4 billion to NIH as part of the American Recovery and Reinvestment Act (ARRA). Annually, about 85 percent of the NIH budget is dispersed by grants and contracts through the 50 states and territories, with a significant impact on the local economies. Economic input-output studies found that through a multiplier effect each Federal dollar of NIH funding generates more than twice as much in state economic output.[3] Moreover, estimates for FY 2007 indicated that NIH grants and contracts supported more than 350,000 jobs, in full or in part.[4] Due to the ARRA funding, we estimate that approximately 50,000 jobs (full or in part) will be created or retained. It is important to note that 2-year ARRA funds will provide job creation and retention as well as longer-lasting impacts from advances in health science. Therefore, this unprecedented infusion of funds has been an excellent opportunity for sustaining our critical investment in medical research while creating jobs, stimulating related economic activity, and also buttressing the competitiveness of the Nation's biomedical research enterprise. The astounding number of applications that we received for ARRA funding (more than 20,000 Challenge Grant applications and 2,000 Grand Opportunity Grant applications)[5] revealed an untapped pool of innovative research ideas and projects with the potential for future breakthroughs and discoveries that address some of the Nation's and world's most pressing health problems. Clearly, NIH serves a unique role as the critical stimulus for the entire U.S. biomedical R&D enterprise.

Five Exceptional Opportunities for Biomedical Research at NIH

The investment in NIH research has certainly paid off. However, we are continuously faced with serious challenges in the fight against disease and disability. I see five major thematic areas that build on NIH's recent advances and that could reap substantial downstream benefits for the diagnosis, prevention, and treatment of a long list of diseases, both rare and common.

First Thematic Area: Applying the unprecedented opportunities in genomics and other high-throughput technologies to understand fundamental biology, and to uncover the causes of specific diseases

In the past, most basic science projects in biomedicine required investigators to limit the scope of their studies to some single aspect of cell biology or physiology. The revolution now sweeping biomedical science is an emphasis on comprehensive approaches that identify *all* of the genes, *all* of the proteins, and *all* of the pathways involved in a disease

process. Technologies contributing to these advances, many of which only recently have become practical to use on a routine basis, include DNA sequencing, microarray technology, nanotechnology, small molecule screening capabilities, new imaging modalities, and computational biology.

Cancer is a prime example of the potential of high-throughput approaches. Although a lot of information has been gleaned in the past from targeted efforts with certain tumors, the first complete cancer genomes are now becoming available (for leukemia and brain tumor). Stunning revelations are emerging about the genetic lesions that are involved in malignancies. Due partly to ARRA funding, The Cancer Genome Atlas is poised to derive comprehensive information about the causes of 20 major tumor types. It is virtually certain that this information will force a complete revision of diagnostic categories in cancer, and will usher in an era when every cancer will be evaluated in this comprehensive way, allowing an individualized matchup of the abnormal pathways in that specific tumor with the specific drug or therapeutic known to target that pathway.

Another example is the exciting new opportunity to understand how interactions between our bodies and the hundreds of trillions of microbes that live on us and in us (the so-called "microbiome") can influence health and disease. The inability to culture most of the species that make up the human microbiome severely limited earlier investigations. But all of these organisms have DNA and/or RNA—and so it is now possible to categorize the vast array of species that are present in various body sites, in both healthy and ill individuals. The consequences for our understanding and treatment of a long list of diseases are likely to be profound. Currently, Human Microbiome Project investigators are studying microbial involvement in a range of diseases including psoriasis, Crohn's disease, ulcerative colitis, and obesity.

Second Thematic Area: Translating basic science discoveries into new and better treatments

Often the path from molecular insight to therapeutic benefit has not been easily or quickly discernible for many disorders. That is changing now. The major factors propelling this change include the discovery of the fundamental molecular defect in hundreds of diseases, new resources that allow the screening of hundreds of thousands of compounds for drugs that target the defective molecule or molecular pathway, and the partnering of academia and industry to bring the strengths of each to the drug development pipeline.

The NIH Therapeutics for Rare and Neglected Diseases (TRND) program, established in FY 2009, is an example of a critical step in the direction of a truly integrated partnership for drug development between NIH and the private sector. TRND will combine experienced, high-level experts from pharmaceutical and biotechnology organizations and academic researchers. These scientists will work together to translate basic research findings into candidate drugs for patients with rare and neglected diseases. This program will allow promising compounds to be taken to the preclinical phase—often referred to as the "Valley of Death" because it is the place where good ideas often die—by modeling its infrastructure and staffing on best practices in the pharmaceutical and biotechnology industries while also capitalizing on the many human, intellectual, and technological resources available at NIH that are not easily accessed by industry.

Another major area that is ripe for major translational advances is the application of various types of stem cells to treatment of human disease. FDA recently approved the first human protocol (for spinal cord injury) involving human embryonic stem cells (hESCs), and the potential for increased Federal support for human embryonic stem cell research will bring into this field many investigators who have been reluctant to participate due to uncertainties regarding Federal funding of research in this area. The recent revelation that skin fibroblasts can be transformed into induced pluripotent stem cells (iPSCs) opens up a powerful new strategy for therapeutic replacement of damaged or abnormal tissues, without the risk of transplant rejection. While much work remains to be done to investigate the possible risks of this approach, there is much excitement about the potential. The development of the iPSC approach stands as one of the most breathtaking advances in basic science in the last several years, and NIH will be making every effort to pursue with maximum speed the therapeutic consequences of iPSCs, hESCs, and adult stem cells.

Third Thematic Area: Putting science to work for the benefit of health care reform

NIH can make substantial contributions to health care reform. For example, in comparative effectiveness research (CER), NIH has supported clinical studies for many years that rigorously evaluate the outcomes of different medical treatment options. Examples include the Diabetes Prevention Program, which demonstrated substantially better benefits of exercise and lifestyle changes over medication in preventing the onset of diabetes, and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which compared older, cheaper antipsychotic drugs with newer ones, demonstrating that the older drugs worked just as well and had a better side-effect profile.

Prevention and personalized medicine is another area where NIH can widely contribute to health care reform. Advances in pinpointing individual genetic and environmental risk factors for disease now make it possible to focus prevention strategies more effectively on those who need them most. For example, including newly derived information about individual genetic risks for colon cancer or prostate cancer in determining the timing of colonoscopy or PSA screening could save lives and save money. Behavioral research focusing on how personalized information about disease risk actually alters health behaviors and clinical outcomes will be a critical component of this program.

Pharmacogenomics is another important area where research can inform health care. Already there is compelling evidence of a correlation between genotype and drug response for more than a dozen drugs, and that number is growing. But prospective studies will be needed for many of these applications, such as the one for warfarin (a widely prescribed anticoagulant), currently underway at NIH. The opportunity to choose the right drug at the right dose for the right person holds great promise for better health, both by avoiding treatments that are not going to work, and by reducing the incidence of adverse drug reactions.

One of the most tragic aspects of our health care system is the widespread presence of disparities in health. The health of racial and ethnic minorities, people living in poverty, people living in rural and remote locations, and other disadvantaged groups in the United States is worse than the health of the overall population. National concerns for these health disparities repeatedly have been expressed as a high priority in national health status reviews (including Healthy People 2010), and attention to this issue will be a critical component of any successful reform of the U.S. health care system. Now, new opportunities are emerging to define the causes and potential solutions for many health disparities, and these call for integration of research on the multifactorial nature of health disparities, including biological and nonbiological factors, and an understanding of the causes of disparities in access to and delivery of health care.

Fourth Thematic Area: Encouraging a greater focus on global health

NIH has a long tradition of supporting research on global health, and recent seminal scientific advances position NIH to make even more important contributions. Examples already in hand include the development of a vaccine against Ebola virus (proven effective in primates) and the recent discovery by NIH researchers of the first new potential drug in 50 years to treat the parasitic disease schistosomiasis.

Much of recent global health research justifiably has been focused on AIDS, tuberculosis, and malaria, given the enormous human toll from these common and life-threatening disorders. NIH is ideally positioned to play a major role in ramping up the discovery phase for these infections, by applying new technologies such as RNAi, high-throughput screening, proteomics, and metabolomics, and tapping into the talents of highly motivated young researchers with a deep understanding of pathogen-host interactions. Combining these technological and human resources will inform future vaccine development and potentially open a vast new range of targets in pathogens and hosts for prevention, diagnostics, and therapeutics. It also is critical to go beyond the focus on the “big three” diseases to apply some of these same strategies to neglected diseases of low-income countries (e.g., roundworm, hookworm, leprosy, African sleeping sickness).

Importantly, we also must respond to the growing challenge of chronic noncommunicable diseases and injuries, which are now responsible for more than half of deaths in the developing world. Studying the causes of diseases such as diabetes and

cancer in countries with limited resources can shed important light on pathogenesis and suggest interventions that can be implemented in low-resource settings.

Fifth Thematic Area: Reinvigorating and empowering the biomedical research community

The lifeblood of biomedical research in the United States rests on the talent and dedication of its scientists and an emphasis on innovation—both factors are considered in NIH's peer review system. The two-level peer review process is much admired and copied by other research agencies around the world. However, the increasing breadth, complexity, and interdisciplinary nature of modern research pose challenges to the traditional review process. To enhance peer review, NIH recently undertook an extensive examination of its review process, and in June 2008, announced a series of concrete steps for improvement. Those include recruiting the best reviewers; shortening proposals to reduce the burden on both applicants and reviewers; adapting the review process to make it as thorough, reliable, fair, and transparent as possible; and focusing more on impact than on methodological details. The effects of these new steps will be closely monitored, and additional reforms that encourage innovation will be undertaken as needed.

NIH-wide innovation now is fostered by the NIH Common Fund, which is designed to support crosscutting innovative projects that require participation of at least two or more Institutes or Centers. Established in law by the NIH Reform Act of 2006, the Common Fund provides a unique opportunity to support research that otherwise might not find a natural home at NIH.

Finally, the success of biomedical research rests squarely on the robustness of NIH training programs for the next generation of basic, translational, and clinical scientists. Multiple issues must be explored including adequacy of support, our role in training foreign scientists, and how best to diversify the scientific workforce. We need to provide the most exciting and positive environment for new scientists possible, where their enthusiasm and creativity will be nurtured in a way that optimizes their scientific creativity and independence.

Conclusion

There are unprecedented opportunities in front of us. The current acceleration in the pace of discovery was unimaginable only a decade ago. We need to capitalize on this moment of great opportunities for biomedical science in order to tackle the maladies that afflict millions of Americans and people around the world. Strong leadership by NIH, in collaboration with the many research organizations in the country and around the world, is a precious asset to the global community to move forward and secure better health and better lives for all.

[1] Manton KG, et al. *PNAS* 2009;106:10981-6. PMID: 19549852. PMCID: PMC2700155.
[2] Zhou F, et al. *Pediatrics* 2002;110(4):653-61. PMID: 12359777.
[3] FamiliesUSA. In Your Own Backyard: How NIH Funding Helps Your State's Economy. Washington, D.C.: 2008. Available at: http://www.familiesusa.org/issues/global-health/publications/in-your-own-backyard.html.
[4] Ibid.
[5] Data as of October 26, 2009.

Overview of NIH Structure and Organization

NIH is the primary Federal agency for leading, conducting, and supporting medical and behavioral research. Its mission is science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability for all Americans and for people worldwide. Composed of the Office of the Director (OD) and 27 Institutes and Centers (ICs), NIH employs close to 19,000 people and is the steward of a $30 billion budget (Fiscal Year [FY] 2009). The leadership and financial support NIH provides to biomedical, behavioral, and social science researchers extends throughout our Nation and the world.

Institutes and Centers

The 27 NIH ICs are organized with a focus on and expertise in 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). The ICs *support* research and research training through extramural activities and most also *conduct* research and research training through intramural activities.

The NIH Reform Act of 2006 reaffirmed certain organizational authorities of agency officials to: 1) establish or abolish national research institutes; 2) reorganize the offices within NIH OD; and 3) reorganize divisions, centers, or other administrative units within an NIH IC. The Act also mandated the establishment of a Scientific Management Review Board (SMRB) to advise the NIH Director and other appropriate agency officials on the use of these organizational authorities, through reports to the NIH Director, at least once every 7 years. Also, any SMRB report that contemplates a specific organizational issue will be submitted to appropriate congressional committees. The SMRB held its first meeting in April 2009 and members were briefed on two topics put forth by senior NIH leadership for their consideration: 1) optimizing research at NIH into substance use, abuse, and addiction; and 2) whether organizational change within the NIH Clinical Center and/or the NIH intramural research program could further optimize those programs. The SMRB unanimously agreed to consider both topics through corresponding workgroups, and to form a workgroup to develop criteria for use in assessing whether specific organizational changes within NIH are warranted. The Board also is required by the NIH Reform Act to seek input from the public. The first two public forums were held in September and October 2009. Workgroup findings will be brought back to the full SMRB for deliberations at future meetings in FY 2010.

Office of the Director

The Office of the Director (OD), NIH, is composed of several offices that provide expert advice to the NIH Director and his leadership team, coordinate policy across the NIH research community, and administer centralized support services essential to the NIH mission. With 229 government-owned buildings in 6 locations, the facilities infrastructure maintained by the NIH 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 a secure and robust information technology infrastructure, the requirements of today's research create greater demands for a safe, healthy, and functional environment for employees and patients.

The NIH Office of Extramural Research (OER) provides the corporate framework for NIH administration of research grants and contracts, ensuring scientific integrity, public accountability, and effective stewardship of the NIH extramural research portfolio. Offices within OER include the Office of Laboratory Animal Welfare, the Office of Policy for Extramural Research Administration, the Office of Extramural Programs, the Office of Research Information Systems, and the Office of Administrative Operations. The Office of Intramural Research (OIR) is responsible for oversight and coordination of intramural research conducted within NIH laboratories and clinics. Offices within OIR include the Office of Intramural Training and Education, the Office of Technology Transfer, the Office of Human Subjects Protection, and the Office of Animal Care and Use. (Also see the section in this chapter on *Extramural and Intramural Research Programs* for more information regarding OER and OIR).

The OD Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) was established by mandate of the NIH Reform Act of 2006. DPCPSI's role is to identify emerging scientific opportunities, rising public health challenges, and scientific knowledge gaps that merit further research; assist NIH in effectively addressing identified areas; and develop and apply resources (databases, analytic tools, and methodologies) that will support priority setting and analyses of the NIH portfolio. In addition, DPCPSI manages the NIH Demonstration Projects in High Risk/High Reward Research—an initiative to test new ways of fostering innovation that also was authorized through the Reform Act. Finally, DPCPSI plans, supports, and provides technical assistance for NIH-wide program and project evaluations and manages NIH planning and reporting required by the Government Performance and Results Act and other government-wide performance assessment endeavors. (Also see the section on *NIH Strategic Planning and the NIH Roadmap and Common Fund* later in this chapter). DPCPSI now incorporates the functions of the former Office of Portfolio Analysis and Strategic Initiatives. The primary components within DPCPSI are the Office of Strategic Coordination, which manages the NIH Common Fund (including the Roadmap), and the four OD program offices—the Office of AIDS Research, the Office of Behavioral and Social Sciences Research, the Office of Disease Prevention, and the Office of Research on Women's Health. Within the Office of Disease Prevention are three offices covering the areas of dietary supplements, rare diseases research, and medical applications of research. The OD program offices fund research using IC award-making authorities. Often, ICs partner with a program office to supplement their funding for a specific program or project.

Other OD offices that advise the NIH Director, develop NIH policy, and provide essential NIH-wide oversight and coordination include the Office of Communications and Public Liaison, the Office of Science Policy, the Office of Legislative Policy and Analysis, the Office of Management, the Office of Equal Opportunity and Diversity Management, the NIH Ethics Office, and the Office of the Chief Information Officer. The policies and activities of some of these offices are highlighted in later sections of this chapter.

Links to IC and OD Office Website Home Pages

Following is a list of NIH ICs and select OD program offices. In the electronic version of the report, the names of the ICs and offices are linked to the home page on the respective websites. 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 in the electronic version, live links to IC and office strategic plans. The mission statements and strategic plans provided in Appendix B classify and justify NIH priorities. Historical information about NIH, including the establishment of the categorical Institutes, Centers, and specialized offices, is maintained by the NIH Office of History, a component of OIR that preserves records of significant NIH achievements, innovative exhibits, and educational programs to enhance understanding of NIH biomedical and behavioral research.

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)[6]
- 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 AIDS Research (OAR)
  - Office of Behavioral and Social Sciences Research (OBSSR)
  - Office of Disease Prevention (ODP)
    - Office of Dietary Supplements (ODS)
    - Office of Medical Applications of Research (OMAR)
    - Office of Rare Diseases Research (ORDR)
  - Office of Research on Women's Health (ORWH)
  - Office of Strategic Coordination (OSC)
- Office of Extramural Research (OER)
- Office of Intramural Research (OIR)

[6] With enactment of the Patient Protection and Affordable Care Act, on March 23, 2010, the National Center for Minority Health and Health Disparities became an institute—the National Institute for Minority Health and Health Disparities (NIMHD).

Extramural and Intramural Research Programs

As noted above, NIH *supports* research and research training through extramural activities and *conducts* research and research training through intramural activities. The sections below provide overviews of the extramural and intramural programs.

Extramural Program

More than $8 of every $10 appropriated to NIH is awarded by the ICs to the extramural biomedical and behavioral research community through grants and contracts. The extramural research community is composed of scientists, clinicians, and other research personnel affiliated with more than 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. In FY 2009, NIH funded more than 37,000 principal investigators on research grants, with many thousands more personnel supported by the projects. With NIH support, these investigators, with their research teams, conduct the vast majority of research that leads to improvements in the prevention, detection, diagnosis, and treatment of disease and disability.

OER is led by the Deputy Director for Extramural Research (DDER), who provides leadership and coordinates policy, guidance, and oversight for IC grant and programmatic management operations and is a conduit for extramural policy issues with the biomedical research community beyond NIH. OER is where grants policy, program coordination, compliance, and services converge to support and sustain the NIH extramural research program.

A primary service OER provides for the NIH grants program is the electronic Research Administration (eRA) system. eRA supports the grant administration functions for grantees and Federal staff from the submittal of applications to close out of awards. eRA also provides services to other operating divisions of the Department of Health and Human Services (HHS) and other Federal agencies. eRA has more than 215 registered users (of which more than 150,000 are principal investigators) at 16,500 research institutions worldwide.

Grants Overview

NIH announces the availability of funds for grant programs by issuing funding opportunity announcements (FOAs)[7] in the *NIH Guide for Grants and Contracts* and on www.Grants.gov. The majority of NIH grant funding is investigator-initiated, submitted through omnibus parent announcements that span the breadth of the NIH mission. NIH uses program announcements (PAs) and requests for applications (RFAs), and other types of FOAs, to express interest in particular areas of research. Because many FOAs are trans-NIH opportunities, considerable collaboration can be involved in their preparation. During 2008 and 2009, NIH refined and further developed an internal electronic document/content management system in support of the *NIH Guide* publication process that facilitates communications, collaborations, and the exchange of documents and information among ICs and within the NIH OD, thereby providing a more efficient and cost-effective means of developing and publishing NIH FOAs.

The main types of grant funding provided by NIH are Research Grants (R series), Career Development Awards (K series), Research Training and Fellowships (T and F series), and Program Projects/Centers Grants (P series). Activity codes that incorporate the funding series differentiate the wide variety of research and research-related awards made by NIH. The most commonly used activity code is the R01, which designates a grant for a discrete, specified research project, generally awarded for 3 to 5 years. Receipt of an R01 traditionally is the mark of a scientist achieving scientific independence, and a faculty member's track record with R01 awards normally is a significant factor in university promotion and tenure decisions. Examples of other activity codes are:

- R41/R42 and the R43/R44 for the Small Business Technology Transfer program and the Small Business Innovative Research program, respectively;
- R24 for research projects that will enhance the capability of biomedical research resources;
- R25 for research education projects;
- F32 for postdoctoral individual fellowships under the National Research Service Award;
- T32 for enabling institutions to make National Research Service Awards for both pre- and postdoctoral training;
- K08, a career development award for providing support and "protected time" to individuals with a clinical doctoral degree for an intensive, supervised research career development experience;
- P01 for research program projects that are broadly based, multidisciplinary, often long-term research, which have a specific major objective or a basic theme;
- P30 for shared resources and facilities at research centers; and
- P40 for animal model and biological materials resources.

ICs vary in the extent to which they use various activity codes.

NIH Peer Review Process

All grant applications and contract proposals for research and development funding undergo evaluation through peer review, in which external expert panels determine which applications or proposals are the most scientifically and technically meritorious—the first tier of peer review—and are most programmatically relevant and therefore should be considered for funding—the second tier of peer review. The NIH peer review process is designed to evaluate the scientific, technical, and programmatic merit of each application for potential research funding with processes that are fair, equitable, timely, and free of bias. The NIH dual (two-tier) peer review system is mandated by statute (section 492 of the PHS Act) and by Federal regulations governing “Scientific Peer Review of Research Grant Applications and Research and Development Contract Proposals” (42 CFR Part 52h).

CSR is the portal for receipt and referral of NIH grant applications and for most applications is the locus for the first level of review. Applications relevant to the NIH mission receive two assignments. One assignment is to an IC that has a mission encompassing the aims and objectives of the application and thus potential interest in funding the application. The other assignment is to the group or panel that will conduct the first level of review, i.e., evaluation of scientific and technical merit. The assignment may be to either a Scientific Review Group (SRG) or a Special Emphasis Panel (SEP). If the application is in response to an RFA, the SRG or SEP most often will be convened by the IC(s) responsible for the initiative. NIH uses established referral criteria to determine the appropriate SRG to carry out review and the IC(s) most suitable to potentially fund the project.

As noted above, the first level of review is conducted by SRGs or SEPs that evaluate and give expert advice on the overall scientific and technical merit of the research proposed in the application, as well as the protection of human subjects, vertebrate animal welfare, and the budget and period of support requested. SRGs and SEPs conducting the first level of review are composed primarily of non-Federal experts qualified by training or experience in particular scientific or technical fields, or as authorities knowledgeable in the various disciplines and fields related to the applications under review. No more than one-fourth of the members of any SRG or SEP may be Federal employees.

The second level of peer review is performed by the National Advisory Councils (or Boards) of each IC, which are composed of scientific and 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- or SEP-reviewed applications assigned to an IC go to the respective Council,[8] 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. Advisory Councils recommend projects for funding, but do not make funding decisions.

An ongoing trans-NIH effort to optimize the efficiency and effectiveness of the NIH Peer Review system is discussed in *Enhancing Peer Review*, under the section below on *Improving Research Management.*

Funding Decisions

Applications that are scientifically meritorious, based on SRG or SEP review, and favorably recommended by an IC's National Advisory Council, are considered for funding. The score given to an application during the initial peer review process is important, but not the sole factor determining an IC's funding decision. Other considerations are portfolio balance, requirements specified in congressional appropriations, programmatic relevance, IC priorities, and availability of funds. (Also see the section later in this chapter on *Enhancing Peer Review* for information on recent changes in the scoring of applications during initial review.)

Many ICs establish a "payline"—a percentile-based[9] funding cutoff point determined at the beginning of the fiscal year by balancing the projected number of applications assigned to an IC with the amount of funds expected by NIH and the IC to be available for such projects. 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.

Prior to award, NIH ensures that the planned research meets all requirements for safe and responsible conduct. This includes making sure that the research has undergone all necessary reviews and has obtained required approvals from boards and committees charged with protection of human subjects; inclusion of minorities, women, and children; humane animal care and use; biosafety; and other matters as appropriate. NIH also ensures that the institution where the research takes place has necessary and appropriate policies in place for avoidance of financial conflicts of interest in research. (Also see the section on *Ensuring Responsible Research* later in this chapter).

Post-Award Administration

NIH policies extend into the post-award phase of research as well, so that NIH can monitor research progress and provide oversight to ensure responsible conduct of research. Scientific monitoring includes reviewing yearly progress and financial reports submitted by grantees, the publications generated by the research, and any invention reports. NIH also monitors compliance with Federal laws and policies pertaining to protection of human subjects, the care and use of vertebrate animals used in research, data sharing, the NIH Public Access Policy, and other matters. In addition, oversight of clinical research may involve data and safety monitoring and tracking of inclusion of women and minorities in research. (Also see the sections on *Capitalizing on Discovery* and on *Ensuring Responsible Research* later in this chapter).

Intramural Research Program

Approximately 10 percent of NIH funds support research and training 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; Detroit, Michigan; Phoenix, Arizona; and the Rocky Mountain Laboratories, Montana. Approximately 1,150 principal investigators lead intramural research projects that involve more than 6,000 trainees ranging from high school students to postdoctoral and clinical fellows. OIR is responsible for trans-NIH oversight and coordination of intramural research, human subject 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 (DDIR), and each IC intramural research program is led by an IC Scientific

Director; OIR oversight is carried out in conjunction with the IC Scientific Directors. A summary of policies governing intramural research can be found in the *Intramural Research Sourcebook*.

Research Programs and Priorities

The NIH intramural research programs conduct basic, translational, and clinical research. Organizationally, the individual laboratories and clinics report to their respective IC and are responsible for conducting original research consistent with the goals of the parent IC. Most ICs have an intramural program, the exceptions being NIGMS, CSR, FIC, and NCRR. As with the extramural program, intramural research proposals are generated by scientists. In the intramural research program, however, program directions and research priorities are not shaped primarily through grant awards,[10] 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, and tenured and tenure-track scientists undergo formal, annual, internal reviews. Resource allocations and promotions are determined from these reviews. In addition, at least every 4 years, an external expert Board of Scientific Counselors 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). Moreover, IC Scientific Directors are evaluated by an external committee every 5 years, and 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.

Two offices manage research training for OIR. The Office of Intramural Training and Education (OITE) is charged with helping trainees in the intramural research program, including graduate students in partnership with universities in the United States and abroad, develop scientific and professional skills to become leaders in the biomedical research community. The Office of Clinical Research Training and Medical Education (OCRTME) deals with all aspects of clinical training. Many training programs were developed or updated during 2008 and 2009 (also see the section on *Research Training and Career Development* in Chapter 3).

NIH Clinical Center

The Clinical Center is the Nation's largest hospital devoted entirely to clinical research. Research at the Clinical Center is conducted with access to cutting-edge technologies in an environment of compassionate care. This world-class national resource promotes translational research—that is, the transformation of scientific observations and laboratory discoveries into applications for diagnosing, treating, and preventing disease that benefit patient health and medical care. Composed of two facilities—the Mark O. Hatfield Clinical Research Center (2005) and the original Warren Grant Magnuson Clinical Center (1953)—the Center houses 234 inpatient beds, 82 day hospital stations, an ambulatory care research facility, 12 operating rooms, critical care facilities, advanced radiology and imaging capabilities, and research laboratories. The unique design of the facility locates patient care units in close proximity to laboratories conducting related research. This design facilitates interaction and collaboration among intramural clinicians and researchers. More than 1,400 studies are in progress at the Clinical Center, bringing 21,000 patients per year from all 50 states and throughout the world. The Center has more than 90,000 outpatient visits a year and 6,000 inpatient admissions. Approximately 1,200 credentialed physicians, dentists, and Ph.D. researchers, 660 nurses, and 630 allied health care professionals, such as pharmacists, dietitians, and medical technologists, work at the Center. As a research facility, generally only a patient with the precise kind or stage of illness under investigation and meeting other inclusion criteria of a protocol is enrolled as a subject in a study. However, in May 2008, NIH launched the Undiagnosed Diseases Program, a clinical research program in collaboration with NHGRI and the NIH Office of Rare Diseases designed to provide answers to patients with mysterious conditions that have long eluded diagnosis by their health care providers. Within its first 6 months, more than 1,000

potential subjects sought to participate in the new program-a tangible reminder that the NIH Clinical Center truly is a “house of hope.”

[7] An FOA is a publicly available document by which a Federal agency makes known its intentions to award grants or cooperative agreements. Funding opportunity announcements may be known as program announcements, requests for applications, solicitations, or parent announcements.
[8] An application may be designated "Not Recommended for Further Consideration (NRFC)" at the first level of peer review, if it lacks significant and substantial merit; presents serious ethical problems in the protection of human subjects from research risks; or presents serious ethical problems in the use of vertebrate animals, biohazards, and/or Select Agents. Applications designated as NRFC do not proceed to the second level of peer review (National Advisory Council/Board) because they cannot be funded.
[9] Percentile represents the relative position or rank (from 1 to 100) of each overall impact/priority score.
[10] The exception is that intramural investigators are eligible to compete for most NIH Roadmap initiatives to allow qualified intramural researchers to contribute to the goals of Roadmap programs.

NIH Strategic Planning and the NIH Roadmap and Common Fund

Strategic Planning

Strategic planning at NIH takes place at many levels. The U.S. Congress, through the NIH authorization and appropriations processes, sets NIH and IC funding levels and directs NIH attention to particular areas of research interest or emphasis.[11] The Administration establishes specific priorities for improving the health of the Nation, such as those in Healthy People 2010, a comprehensive set of disease prevention and health promotion objectives aimed at increased quality and years of healthy life and the elimination of health disparities for the Nation. Through progress reviews, HHS tracks trends in data that measure advancement toward the plan's objectives. NIH efforts are contributing toward Healthy People 2010 objectives, ranging from reducing uncorrected visual impairment due to refractive errors to increasing the proportion of persons with arthritis who have had effective, evidence-based arthritis education as part of management of their condition. Healthy People 2020 objectives are now in development, and will reflect assessments of major risks to health and wellness, changing public health priorities and emerging issues related to our Nation's health preparedness and prevention that also will need to be addressed by NIH. In addition, NIH establishes its own goals and priorities fully cognizant of the framework of the *HHS Strategic Plan Goals and Objectives* - FY 2007-2012, which sets the stage for individual performance plans and outcome measures across NIH.

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 can serve as a framework for ICs to measure and report on portfolio balance and progress relative to their missions. NIH stays constantly tuned to twin touchstones for priority-setting—public health need and scientific opportunity.

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 generating 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, and various FOAs—to move science planning into the implementation stage. Finally, strategic plans influence IC priority-setting and funding decisions.

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 working groups that contain recommendations for research goals or priorities within the IC mission.

NIH also has a significant tradition of trans-NIH strategic planning, which has been strengthened through the creation of DPCPSI in the NIH OD. DPCPSI was created to identify important areas of emerging scientific opportunity, rising public health challenge, and knowledge gaps that deserve special emphasis and would benefit from strategic coordination and planning or the conduct or support of trans-NIH research that involves collaboration between two or more national Institutes or Centers. As noted above, DPCPSI is the organizational home for the NIH Common Fund (see section below on *Common Fund Strategic Planning Processes*). Another important facet of DPCPSI's role in support of NIH-wide planning and coordination is its development and application of resources (e.g., databases, analytic tools, and methodologies) in support of portfolio analyses and priority setting.

Trans-NIH strategic plans focus on areas that are best addressed by involving multiple ICs in identifying research goals and priorities. A prominent example is the annual *Trans-NIH Plan for HIV-Related Research* to guide the NIH investment

in biomedical and behavioral AIDS-related research and to provide the framework to translate critical research findings into improved prevention and treatment strategies. The development of the plan is led by OAR, using a collaborative process involving broad input from scientists across NIH, other government agencies, and non-governmental organizations, as well as community representatives and other experts from the United States and abroad. Another example is the March 2009 Report, *Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases*—a 10-year plan for digestive diseases. The Commission was led by NIDDK and was composed of 16 members, including academic researchers, medical professionals, and patient advocates, who were appointed by the NIH Director, and 22 representatives of NIH ICs, as well as other Federal agencies involved in digestive diseases research, who served as *ex officio* members. Other trans-NIH research plans address goals and objectives in areas that include neuroscience research, liver disease, diabetes, health disparities, muscular dystrophies, autoimmune diseases, and more. (Lists of both IC and trans-NIH strategic plans appear at the end of each disease/disorder topic section of Chapter 2).

Common Fund Strategic Planning Processes

The NIH Common Fund was established by the 2006 Reform Act to support the mission of NIH. The trans-NIH strategic planning for the Common Fund occurs continually and on many levels. The most visible activity occurs every 3 to 5 years and was first initiated before the Common Fund existed as a process to address fundamental barriers to research or unique opportunities that affect the NIH mission as a whole. The programs that resulted from these early planning processes are known collectively as the NIH Roadmap for Medical Research. With the establishment of DPCPSI and the Common Fund, the goals for the Roadmap have been maintained, but the planning activities have been expanded to increasingly foster inter-IC collaboration and coordination and to allow the NIH Director added flexibility to develop new programs continually rather than only on a 3- to 5-year schedule.

NIH uses iterative planning processes, involving NIH stakeholders and NIH leadership, to generate, select, prioritize, and develop recommendations for Common Fund initiatives. Various assessments and portfolio analyses, supported by new and evolving databases, analytic tools, and evaluation methodologies, inform the planning processes. NIH solicits 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 criteria established for Common Fund initiatives (see text box). This solicitation is conducted formally every 3 to 5 years through an expanded process involving brainstorming workshops, Requests for Information, and widespread staff involvement. In other years, ideas are presented to the NIH Director through continual interaction with IC directors and leaders in the scientific and lay communities. As required by the Reform Act, on a biennial basis, NIH issues a Common Fund Strategic Planning Report. The latest such report, issued in June 2009, is provided in Appendix C.

To facilitate the prioritization of ideas, NIH conducts a programmatic review of the ideas that are gathered—assessing their responsiveness to the Roadmap initiative criteria, as well as conducting a preliminary assessment of the currently funded NIH portfolio of research related to the broad areas highlighted by the ideas presented. Informed by this analysis and following scientific discussion with IC directors, the NIH Director selects areas that are to be pursued. Trans-NIH Working Groups then form to develop funding announcements and to implement programs in the selected areas.

A Council of Councils,[12] also established by the Reform Act, advises the NIH Director on scientific areas pursued through the Common Fund and considers concepts for new Common Fund programs.

Criteria for Common Fund Initiatives

The goals established for Common Fund initiatives by the 2006 Reform Act include identifying research that:

- Represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps
- Deserves special emphasis
- Would benefit from conducting or supporting additional research that involves collaboration between two or more national research institutes or national centers, or otherwise benefit from strategic coordination and planning.

In addition to these criteria, NIH expects Common Fund programs to:

- Have the potential for exceptionally high impact and accepts a high level of risk that may be associated with innovation and creativity
- Catalyze research funded through the ICs and to synergize with IC program

[11] For more information see http://officeofbudget.od.nih.gov/pdfs/FY09/Significant%20Items%20Final.pdf and http://officeofbudget.od.nih.gov/pdfs/FY10/Significant%20Items.pdf.

[12] The Council of Councils is composed of approximately 30 members selected from the IC National Advisory Councils and nominated by the OD program offices, as well as broad lay representation, including a member of the NIH Council of Public Representatives. The Council advises the NIH Director on matters related to the policies and activities of DPCPSI, and acts as an external advisory panel to the IC directors during the "concept approval" stage of the Common Fund/Roadmap initiative review process through its recommendations to the NIH Director and DPCPSI Director.

NIH Implementation of the American Recovery and Reinvestment Act of 2009 (Recovery Act)

The American Recovery and Reinvestment Act (ARRA) of 2009 (Pub. L. No. 111-5) was signed into law by President Obama on February 17, 2009. The legislation provided NIH with an unprecedented level of additional funding $10.4 billion to help stimulate the U.S. economy through the support and advancement of scientific research.[13] Although NIH has broad flexibility to invest in many types of grants programs, the ARRA-funded projects aim to stimulate the economy and create or retain jobs, and have the potential for making scientific progress in 2 years. The impact of NIH ARRA funding is expected to extend beyond the investigators who receive the funds to also reach allied health workers, technicians, students, trade workers and others who will receive the leveraged benefits. Beyond the immediate economic stimulus, the long-term impact from the science projects, research training, and research facilities funded by the Recovery Act will have a positive impact on the health of the Nation for years to come.

NIH quickly developed implementation and spending plans for the $10.4 billion in 2-year ARRA funding initiatives, and between March 4 and September 18, 2009, published 22 Recovery Act FOAs. The response from the scientific community was extraordinary. Typically the CSR reviews 16,000 applications with the help of about 8,000 reviewers in each of NIH's three annual rounds of review. In 2009, in one round, CSR assessed about 40,000 applications (including ARRA applications), relying on the assistance of about 28,000 reviewers.

The bulk of the ARRA funds—$8.2 billion—will be used for extramural awards for scientific research. In FY 2009, NIH funded $4.73 billion in grants and contracts to universities, medical centers, hospitals, and research institutions throughout the country. Nearly 60 percent of ARRA funds are supporting new science, while approximately 40 percent of funds are accelerating the science of existing projects. Because of ARRA funds, over two summers approximately 5,000 students and science educators will gain hands-on experience in top research laboratories. Approximately $137 million in ARRA funds were transferred from the NIH OD to the Common Fund to support and expand existing Roadmap programs and to address cross-cutting emerging needs and opportunities outside the Roadmap. (See also the section of this chapter on *Strategic Planning and Common Fund/Roadmap*.) One billion dollars in NIH Recovery Act funds was provided to NCRR specifically for the Extramural Construction program. Other approximate allocations are: $500 million for NIH buildings and facilities; $300 million for the shared instrumentation grant program; and $400 million for comparative effectiveness research (CER),[14] which can be awarded through a variety of mechanisms including Grand Opportunity Grants, Challenge Grants, R01s, and supplements. (Also see the section on *Clinical and Translational Research* in Chapter 3 for more information about CER).

ARRA Funding for Extramural Scientific Research

For the $8.2 billion in Recovery Act funds for extramural research projects, NIH is implementing a strategy that focuses on:

1. Expansion of the payline to support peer-reviewed and approved, highly meritorious, grant applications from investigators across the Nation for whom funding was not available in FY 2008, as well as grant applications not otherwise likely to be funded in FY 2009 or FY 2010 because of budgetary limits.
2. Revision Applications/Administrative Supplements to expand the scope and accelerate the tempo of ongoing science through support of additional infrastructure and personnel on existing awards for additional activities that fit the intent of ARRA.

3. Challenge Grants to focus on health and science problems in 15 broad areas of scientific interest where significant progress can be made in a 2-year timeframe. Within each area, specific Challenge Topics were identified. NIH spent more than $380 million in FYs 2009/2010 ARRA funds to support more than 800 grants.
4. Grand Opportunity Program or "GO grants" to support high-impact ideas that lend themselves to short-term, non-renewable funding, and may lay the foundation for new fields of investigation. The GO program supports large-scale research projects costing more than $500,000 each that accelerate critical breakthroughs, early and applied research on cutting-edge technologies, and new approaches to improve the synergy and interactions among multi- and interdisciplinary research teams. NIH spent more than $600 million in FYs 2009/2010 ARRA funds to support more than 350 grants.
5. Signature Initiatives to support new, exceptionally creative, innovative, and potentially transformative scientific opportunities in major research challenges, such as nanotechnology, health disparities, autism, genetic risk for Alzheimer's disease, and HIV vaccine research.
6. New Faculty Awards to support the recruitment of faculty to conduct research at U.S. institutions.
7. Summer Research Experiences for Students and Science Educators to provide summer jobs for high school/college students and teachers to work in science laboratories. These supplements encourage students to seriously pursue research careers in the health-related sciences and support student research experiences in NIH-funded laboratories. Awards were made to approximately 350 institutions (including small businesses), supporting 1,300 mentors, and providing about 5,100 summer research positions for 4,400 students and 700 teachers.

NIH began making Recovery Act awards in April 2009. About half of the ARRA funding available for the extramural scientific research was obligated in FY 2009, with the rest to be obligated in FY 2010. NIH grant awards funded by the Recovery Act have been made in all 50 States, the District of Columbia, and Puerto Rico.[15]

ARRA Funding for Extramural Construction

Recovery Act funds for extramural construction ($1.0 billion) are building the Nation's capacity to conduct biomedical and behavioral research by providing support to domestic health professional schools, other academic institutions, hospitals, health departments, and research organizations. Funds are being used to improve facilities to meet the biomedical or behavioral research, research training, or research resource needs of an institution. Awardees must consider the use of "green" technologies and design approaches, and certain projects must obtain certification from the U.S. Green Building Council's Leadership in Energy and Environmental Design (LEED) or the Green Building initiative's Green Globes System Certification rating. NIH ARRA funding for extramural construction supports two main activities:

1. The Extramural Research Facilities Improvement Program to expand, remodel, renovate, or alter existing facilities, or to construct new facilities, for biomedical and behavioral research.
2. The Core Facility Renovation, Repair, and Improvement activity awards to renovate, repair, or improve core facilities, which are centralized shared resources that provide access to instruments or technologies or services, as well as expert consultation to multiple investigators supported by the core.

ARRA Funding for Shared Instrumentation

The Recovery Act Shared Instrumentation program ($300 million) aligns with the existing Shared Instrumentation program, and provides grants to NIH-supported research institutions to provide multiple investigators with technologically sophisticated equipment to enable the conduct of federally sponsored research. The Shared Instrumentation program consists of two main activities:

1. The Shared Instrumentation Grants program supports grants to groups of three or more NIH-supported investigators for the purchase of commercially available instruments, such as confocal and electron microscopes, biomedical imagers, mass spectrometers, DNA sequencers, biosensors, and cell sorters costing from $100,000 to $500,000.
2. The High-End Instrumentation Grants program supports grants to groups of three or more NIH-supported investigators for the purchase of a single major item of biomedical research equipment costing from $600,000 to $8,000,000. Examples of such equipment include high-resolution mass spectrometers, cryoelectron microscopes, and supercomputers.

Awards are made to public and non-profit domestic institutions only, including health professional schools, other academic institutions, hospitals, health departments, and research organizations.

ARRA Funding for NIH Buildings and Facilities

The intended recipients of ARRA funding for NIH buildings and facilities ($500 million) are construction contractors. Awards are made through new or existing competitive contracts. Several major projects will be supported with Recovery Act funds:

1. John Edward Porter Neuroscience Research Center Phase II to complete the consolidation of neuroscience researchers into one facility from 10 Institutes and multiple disciplines.
2. Building 10 F Wing Renovations to support translational research for 9 of the 12 ICs that have clinical research programs in the new Clinical Research Center.
3. Build-Out of Building 3 to transform an unused, vacant building that could not be reoccupied as laboratory space into useable office space.
4. Conversion of Building 7 at the Rocky Mountain Laboratories in Hamilton, Montana, to convert unused mechanical space to laboratories, providing critical space for NIAID research.
5. Other Repair and Improvement Projects to improve the reliability and condition of NIH facilities.

Examples of specific ARRA funded activities are highlighted throughout the report in the topic sections that follow in Chapters 2 and 3.

Oversight

NIH implementation of ARRA is accompanied by an unprecedented level of oversight and reporting to ensure that Recovery Act funds are being used in accordance with legal and administrative requirements, and to provide the public with up-to-date data on the expenditure of funds. NIH activities include:

Performance Measures

NIH fully complies with all Recovery Act monitoring and reporting requirements, including monthly and quarterly reports. Moreover, NIH has established performance measures for the Recovery Act programs in extramural construction, buildings and facilities, shared instrumentation, and extramural scientific research. The measures are posted as part of the implementation plan for each funding area under “Strengthening Scientific Research and Facilities” on the HHS page of the Recovery Act website. In addition, NIH has developed scientific research outcome and output goals for its ARRA funding. Details and data regarding the goals will be included in the FY 2011 and FY 2012 NIH Budget Requests.

Monitoring

In addition to established NIH policies, procedures, and oversight practices that monitor NIH grants, cooperative agreements, and contracts in accordance with established law and policies,[16] the NIH Office of Management Assessment

(OMA) and the Office of Financial Management will use the established NIH risk management framework for identifying, assessing, and testing of operational and financial risks and internal controls associated with implementing Recovery Act requirements.[17] OMA will work with NIH offices responsible for implementing programs receiving Recovery Act funding, and report on the risks and controls to NIH and HHS leadership. The Division of Environmental Protection in the NIH Office of Research Facilities reviews the environmental plans and monitors compliance for all extramural construction awards. All Recovery Act funds are awarded separately from normal appropriations funds, and all awards issued with Recovery Act funds have special accounting numbers and codes to track the funds and awards.

Transparency

Recipients are kept informed of their reporting obligations—both existing NIH and Recovery Act reporting requirements—through special terms and conditions of award, administrative notices in the *NIH Guide* FOAs, contract solicitations, and program guidance. Further technical assistance is available to grantees and contractors from project officers and OER to ensure compliance with reporting requirements. Beginning in October 2009, recipients of ARRA funds are required[18] to submit quarterly reports through the www.FederalReporting.gov website. These reports contain detailed information on the projects and activities funded by the Recovery Act.[19] These reports are available to the public on www.Recovery.gov. NIH developed and provided outreach, oversight, and data quality reviews for the quarterly recipient reports required by the Recovery Act.

Accountability

In addition to the monitoring and oversight actions described above, the NIH performance appraisal system for program and business function managers incorporates Recovery Act program stewardship responsibilities, as appropriate, to ensure that managers are held to high standards of accountability in achieving program goals under the Recovery Act.

[13] Information about NIH ARRA-funded projects and their impact on the economy in terms of jobs created and retained is available at www.hhs.gov/recovery.

[14] Comparative effectiveness research is the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in "real world" settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances. To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations and sub-groups. Defined interventions compared may include medications, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, and delivery system strategies. This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness and actively disseminate the results.

[15] See http://report.nih.gov/recovery/index.aspx for a listing.

[16] Guidance includes OMB Circular A-110, OMB Circular A-123, *Management's Responsibility for Internal Control*, sections of the Recovery Act including Section 1512, and the *Updated Implementing Guidance for the Recovery Act of 2009.*

[17] Assessments will be done consistent with the statutory requirements of the Federal Manager's Financial Integrity Act, the Improper Payments Information Act, and the OMB circular A-123 *Management's Responsibility for Internal Control*.

[18] Section 1512 of the Recovery Act.

[19] OMB Memorandum M-09-21, Implementing Guidance for the Reports on Use of Funds Pursuant to the American Recovery and Reinvestment Act of 2009. June 22, 2009. Available at: http://www.whitehouse.gov/omb/assets/memoranda_fy2009/m09-21.pdf.

Providing the Platform for Discovery

Science Education and Literacy

NIH takes an active role in pre-college (K-12) science education and in science literacy activities. These activities aim to improve the science knowledge and skills of students, 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 350,000 curriculum supplements upon request to K-12 educators across the Nation. Topics covered include "The Science of Healthy Behaviors," "Cell Biology and Cancer," and "The Brain: Understanding Neurobiology through the Study of Addiction." The newest addition is "Exploring Bioethics" for high school biology classes.

NIH provides other types of school resources as well. *Findings* is a semi-annual magazine targeted to high school and early college students to convey the excitement of cutting-edge research, the interesting people who pursue science careers, and the enjoyment they get from this work. A companion website offers videos, podcasts, and interactive games expanding on the printed material. NIH also offers topical publications and school resources such as slide kits, online quizzes, and science puzzles that are used by teachers across the country to augment textbooks and enrich the classroom experience. Subject areas include cell biology, genetics, structural biology, chemistry, pharmacology, and computational biology. Classroom posters linked to selected publications also promote interest in science and research careers, and continue to be tremendously popular.

NIH aims to engage students and the public in the wonders of biology and biomedical research through other programs as well. For those who are interested in a career in the life sciences, NIH provides resources such as LifeWorks®, a career exploration website for middle and high school students, and their parents, teachers, and career guidance counselors. Users can search the site for in-depth information on more than 100 health and medical science-related careers, 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 Award (SEPA) program 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. SEPA generates resources such as curricula, exhibits, films, and after-school and summer hands-on science programs. The SEPA website provides access to the educational materials and expertise produced through these efforts.

Information and Information Technology

The goal of Information and Information Technology (I&IT) at NIH is to provide a platform for discovery through advanced tools, systems, and IT infrastructure, so that knowledge creation, discovery, and collaboration are commonplace through the NIH biomedical community. NIH has evolving research and business needs, which require effective and responsive design, management, and implementation of I&IT assets so that the most benefit is gained pursuant to the NIH mission.

In January 2008, in an effort to foster improved I&IT efficiencies, integration, and oversight, the Office of the Chief Information Officer (OCIO) was established in the NIH OD, and the functions of the Chief Information Officer (CIO) were transferred from the NIH Center for Information Technology (CIT). OCIO develops IT-related strategy, services,

and policy to ensure that all NIH IT infrastructure is secure, cost-effective, responsive, and benchmarked against industry standards.

CIT functions as the operating arm of the CIO, and provides expertise and support for OCIO program activities. CIT supports NIH research and management programs with efficient, cost-effective, administrative and high-powered scientific computing, software development, networking, and telecommunications services. CIT directs Business Intelligence Services (known as nVision) to provide a central data reporting repository for data extracted from systems that manage the day-to-day operations of NIH. nVision provides reporting tools to meet NIH business needs, including ARRA reporting and monitoring capabilities.

From supercomputing to management of an Image Processing Facility, CIT provides the NIH intramural community with invaluable tools and resources, such as bioinformatics support, and CIT's scientists, engineers, and mathematicians, as partners in the discovery of biomedical knowledge, contribute to advances in computational science. CIT also deployed and now manages the NIH Federated Authentication Identity Service (known as iTrust), which facilitates access to NIH research applications, databases, and scientific information, by authorized collaborators from government agencies, national laboratories, universities, hospitals, and pharmaceutical and biotechnology medical research centers, using the same sign-in as their home institution. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3).

Infrastructure and Capacity-Building

Many research resource, infrastructure, and capacity-building activities are addressed in the chapters that follow. These include investments in informatics and research resources such as data repositories and disease registries; funding of shared instrumentation; funding of programs that support development and use of animal models; clinical research networks and centers for clinical and translational research; and efforts to increase and enhance capacity for research on minority health and health disparities (see respectively the sections on *Disease Registries, Databases, and Biomedical Information Systems; Technology Development; Molecular Biology and Basic Sciences;* and *Clinical and Translational Research* in Chapter 3 and the section on *Minority Health and Health Disparities* in Chapter 2). However, several important additional infrastructure and capacity-building activities are cross-cutting and do not fit neatly into these sections of the report so are noted here.

The Institutional Development Award (IDeA) program broadens the geographic distribution of NIH funding for biomedical and behavioral research. By supporting faculty development and research infrastructure enhancement, the program enhances the competitiveness of investigators at institutions located in States that historically have been less successful in competing for NIH funds. IDeA also serves unique populations, such as rural and medically underserved communities where it is active—currently 23 states and Puerto Rico.

NIH's interest in capacity-building extends beyond our Nation's borders. For example, there is a growing recognition of the scientific imperative and mutual health benefit of a stronger research environment in Sub-Saharan Africa. To address the need to build stronger and more sustained partnerships with African institutions, in November 2008, NIH held a summit on Sub-Saharan Africa. This seminal meeting provided a forum for discussing key opportunities for expanding research activities between NIH and Sub-Saharan Africa institutions, with the goal of identifying prospects for enhancing NIH research, while working to stimulate the scientific research enterprise in Sub-Saharan Africa, bolstering the growth of centers of excellence in Sub-Saharan Africa, and encouraging the development of a cadre of African investigators able to advance a research agenda for the region. As follow-up to this summit, and in an effort to expand its support of research and research training involving African institutions and scientists, NIH published a notice in the NIH Guide for Grants and Contracts encouraging African scientists and institutions to become involved in its various research and research training programs that offer the opportunity to contribute to science while building research capacity at African scientific institutions.

Core facilities are increasing in number, complexity, and cost. At the same time, there are academic institutions that are in need of the services of core facilities but cannot readily access them. To address these issues, NIH launched efforts directed toward the efficient management and utilization of core facilities, including a 2-day meeting held in July 2009. NIH already is taking steps to implement the recommendations made by scientists and administrators who attended the meeting.

Public-Private Partnerships

The NIH Program on Public-Private Partnerships

The NIH Program on Public-Private Partnerships (PPP), within the NIH Office of Science Policy, was established in 2005 as an NIH Roadmap initiative to facilitate collaborations to improve public health through biomedical and behavioral research. As the central NIH resource on public-private partnerships, the program staff provide guidance and advice to ICs and OD offices and to potential partners on the formation of collaborations that leverage NIH and non-NIH resources to achieve synergy. Program staff work with ICs and OD offices to review existing partnership mechanisms and to recommend policies or legal authorities needed to achieve NIH objectives, manage intellectual property, achieve data access and sharing, and address human subject protections and other critical and complex concerns in the setting of PPPs. NIH PPPs are science-driven, aim to improve the public health, and are structured to uphold the principles of transparency, fairness, inclusiveness, scientific rigor, and compliance with Federal laws and NIH policies. The PPP Program is responsible for the NIH Manual Chapter on Public-Private Partnerships—a reference guide to using the various available mechanisms to create public-private partnerships.

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) (see below for more information on FNIH). One example of a PPP is the Genetic Association Information Network (GAIN)—a combined private sector, FNIH, and NIH effort to provide genome-wide association data for common diseases. GAIN completed its work in 2008 and posted genotypes and phenotypes from the 18,000 samples it mapped to the NLM database of Genotypes and Phenotypes (dbGaP). Another PPP example is the Biomarkers Consortium—a complex partnership involving NIH, the U.S. Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services, FNIH, the Pharmaceutical Research and Manufacturers of America, and the Biotechnology Industry Organization. The Biomarkers Consortium is dedicated to discovery, development, and regulatory qualification of biomarkers[20] in any area of biomedicine.

The PPP Program also is involved in the development of international partnerships in several ways: international memberships and participation in the Biomarkers Consortium; membership and active participation in the National Academies Government-University-Industry Roundtable International Agreements group; providing advice and best practices in consultation with other governments seeking to establish PPP policies and programs (Canada and others); and ongoing conversations with leadership in the European Union's Directorates-General of Research as well as Enterprise and Industry. The expected outcome of these activities is to increase the involvement and harmonization of global activities in biomedical research consortia and collaborations.

The Foundation for the NIH (FNIH)

FNIH is an independent, private, charitable foundation established by Congress to support the NIH mission. A non-profit, 501(c)(3) corporation, the foundation works to engage the private sector, public and patient advocacy organizations, and researchers in cross-sector and multidisciplinary activities for a broad portfolio of unique programs that complement and enhance NIH priorities and activities. As a non-governmental entity, FNIH is not subject to a variety of policies and regulations that NIH as an agency of the U.S. Government is bound by, thus allowing FNIH to have a unique role in PPPs including raising funds for NIH initiatives and activities.[21] This enables NIH to leverage private sector partners' energy, ideas, and other resources in many promising research collaborations that might not otherwise be undertaken by any of the partners alone due to cost, risk, or other reasons. Although some FNIH partnership initiatives involve one specific IC,

many involve two or more with a trans-NIH focus, including efforts on cancer, neuroscience, proteomics, informatics, and imaging.

FNIH manages large-scale programs, such as the Grand Challenges in Global Health Initiative, as well as highly focused programs such as special fellowships, lectures, and conferences. Much of the foundation's focus is on identifying partners (including organizations and individuals) and matching donors' interests to specific NIH needs. However, corporations, individuals, or foundations can bring an idea to FNIH, which then works with donors to assess which of the extraordinary array of existing and prospective programs within NIH's priorities would be most relevant to their interest.

All FNIH activities support the NIH mission, and include activities that, for example, help in developing new trial methodologies or tools, or new datasets. NIH's OSP serves as the official NIH liaison to FNIH, and maintains a record of each Memorandum of Understanding between NIH ICs and FNIH.

[20] Biomarkers are any characteristic that can be objectively measured to indicate (that is serve as a surrogate of) normal biological processes, disease processes, or responses to therapeutic intervention. Biomarkers are the foundation of evidence-based medicine, promising to revolutionize the development and use of therapeutics, and to make the practice of medicine more personalized, predictive, and preemptive.
[21] In 2008, for the third consecutive year, Charity Navigator gave a coveted four-star rating to the Foundation for NIH and recognized it as the #1 health charity.

Improving Research Management

Enhancing Peer Review

Starting in 2007, NIH conducted a year-long, formal self-assessment of its peer review system. This assessment aimed to maintain the hallmarks of objectivity, fairness, and maximum competition that form its foundation, while accommodating the growing breadth, complexity, and interdisciplinary nature of modern research. The assessment involved recommendations from external and internal working groups, feedback from advocacy groups and regional town hall meetings, and consultation with professional societies. The final report, issued in March 2008, outlined broad challenges, and recommended transformative enhancements of the NIH peer review system. Subsequently, NIH convened internal committees to outline strategies and timelines to achieve implementation goals in four broad priority areas:

- Engage the best reviewers
- Improve the quality and transparency of review
- Ensure balanced and fair reviews
- Engage in continuous review of peer review

Figure 1-1: Timeline for Enhancement of the NIH Peer Review Process

In spring 2008, NIH engaged in a detailed, intense, and rapid planning process (see Figure 1) to implement and launch the enhancements. The first changes—adjustments to recognize early stage investigators—were launched in less than a year. The changes began rolling out quickly thereafter and were accompanied by extensive training sessions and communication efforts. Remarkably, the advent of ARRA funding sped rather than slowed implementation. NIH used the new shorter application form for ARRA research grant applications in advance of the scheduled NIH-wide implementation of this enhancement. Other planned enhancements launched on their original timelines.

The peer review enhancement process entailed numerous policy announcements (see Table 1).

Table 1-1: Enhancing NIH Peer Review: Selected Policy Announcements

NOT-OD-09-024	NIH Announces New Scoring Procedures for Evaluation of Research Applications Received for Potential FY 2010 Funding
NOT-OD-09-025	NIH Announces Enhanced Review Criteria for Evaluation of Research Applications Received for Potential FY 2010 Funding
NOT-OD-09-003 and NOT-OD-09-016	New NIH Policy on Resubmission (Amended) Applications
NOT-OD-09-013	Revised New and Early Stage Investigator Policies

Following are highlights of the enhancements made within each priority area.

Engage the Best Reviewers

- New members of scientific review groups were given additional flexibility regarding their tour of duty. They now can expand their period of service preparing for and attending fewer meetings per year over a longer period of time. NIH expects that this option for flexibility will make it easier for reviewers to serve on scientific review groups.
- The Scientific Review Officers who staff SRGs and SEPs now have guidance on best practices for recruiting reviewers.
- NIH is conducting pilot tests of the use of high-bandwidth technological support for review meetings (such as virtual participation via videoconference) to provide reviewers with alternatives to in-person meetings, which require considerable time investments for travel.
- NIH implemented a policy for continuous submission of certain applications from appointed members of chartered NIH advisory groups and frequent temporary members (SRGs and Advisory Councils). Under the continuous submission policy, eligible applicants can submit their R01, R21, and R34 applications continuously (without regard to deadlines). The applications are reviewed by a SRG or SEP no later than 120 days after receipt and then are referred to the appropriate Advisory Council for the final level of review at its next meeting. This benefit is provided as part of the NIH continuing commitment to recognize outstanding peer review service. The first use of the continuous submission policy, in February 2008, was so successful that, in July 2009, it was extended to ad hoc members of advisory groups.

Improve the Quality and Transparency of Review

- NIH began using enhanced review criteria to evaluate research grant applications submitted for potential FY 2009 funding. The enhanced review criteria emphasize the potential impact of the work proposed and de-emphasize details of the experimental design with the intention of improving the quality of review. The enhanced review criteria form the basis for ongoing efforts to align the application format with the review criteria, which will greatly facilitate the transparency of the review process.
- NIH implemented a new 1-9 scoring system, in lieu of the current 41-point scale. Moreover, instead of giving the application just one score, each assigned reviewer also gives a numerical score for each of the now enhanced review criteria. For most applications, the criteria are significance, investigator(s), innovation, approach, and environment. Additional review criteria may be added for applications submitted in response to RFAs and certain Program Announcements. The nine-point scale is designed to provide an optimum range for making reliable and meaningful distinctions among applications.
- Reviewers are using structured templates to compose their critiques of the applications they review. The template focuses the review on the application's strengths and weaknesses relative to each criterion and fosters more concise and clear communication of the reviewer's assessment.
- Applications have been shortened and restructured. Applications submitted on and after January 25, 2010, are organized to align with the structure and content of the enhanced review criteria. This helps ensure that review and applicant expectations coincide for a more efficient and transparent process. At the same time, NIH shortened the page limits for certain sections of applications. This both reduces burden and focuses applicants and reviewers on the essentials of proposed research plans.

Ensure Balanced and Fair Reviews across Scientific Fields and Career Stages, and Reduce Administrative Burden

- To ensure that the largest number of high-quality and meritorious applications receive funding earlier and to improve system efficiency, NIH decreased the number of allowed grant application resubmissions (amendments) from two to one.
- Where possible, NIH is clustering New Investigator and Early Stage Investigator[22] applications during review, and the same approach was extended to clinical research applications.
- The standard review criteria used by reviewers to evaluate applications for research grants and cooperative agreements were enhanced (see *Improve Quality and Transparency of Review* above) to include consideration of the investigator's career stage.

Continuous Assessment of Peer Review

- Ongoing evaluation is critical to the health of the NIH peer review system and assuring that the system embodies the core values of competence, fairness, timeliness, and integrity. To achieve this end, NIH operationalized a dynamic effort to assess the cumulative outcomes of the changes being brought about by the peer review enhancements. This is part of a larger effort to develop appropriate measures and indicators for future monitoring efforts.

Launching RePORT: A Central Portal for Information on NIH Research Activities

NIH is committed to promoting a high level of public accountability for its investment of public funds. As part of that effort, NIH strives to provide extensive, detailed, and accurate information on its research funding in a user-friendly format. To that end, the Research Portfolio Online Reporting Tool (RePORT) was created by OER. RePORT serves as the central repository for all NIH external reports and as a public access point for comprehensive information, data, and analyses of NIH research activities. This includes information on NIH expenditures and the results of NIH-supported research, as well as a section on reports specific to recent issues of interest, such as the Recovery Act. To facilitate and encourage public use of RePORT, a tutorial introducing the major features of RePORT is presented on the site.

The RePORT home page provides links to frequently requested information and to major sections of the site, including:

- The NIH Data Book, which provides basic summary statistics on extramural grants and contract awards, grant applications, the organizations NIH supports, the scientific workforce, and trainees and fellows supported through NIH programs. NIH Data Book charts and tables are generated and updated automatically from a database of NIH statistics and can be exported to PowerPoint or printed in a printer-friendly format.
- NIH Strategic Plans, a site that provides links to strategic plans including IC, NIH-wide, topical, and HHS and inter-agency plans, with information on plans in the process of being updated.
- Categorical Spending, which provides the link to and information about the NIH Research, Condition, and Disease Categorization (RCDC) system. (See section immediately below for more information.)
- RePORT Expenditures and Results (RePORTER), NIH's new and improved searchable database of funded research projects. (See section below—RePORTER: Expanded Information on Scientific Projects—for more information.)
- The Reports page, which provides access to a searchable database of reports. Each report has been categorized by topic, IC, the portfolio being reported on, the budget mechanisms and activities through which the programs included in the report are funded, and the years covered by the report. There are several drop-down menus that can be used to narrow the search further, which reduces the database containing hundreds of reports to a small set that matches the selected criteria.
- Other information, including this report—*The Biennial Report of the Director, National Institutes of Health*.

Research, Condition, and Disease Categorization (RCDC) System

In mid-January 2009, NIH launched a new process for providing detailed funding information, by fiscal year, for 215 major research categories, as part of its extensive efforts to keep the American people informed about how their tax dollars are used to support biomedical and behavioral research. The process, known as Research, Condition, and Disease Categorization (RCDC), uses a computerized approach to mine the descriptive text associated with NIH research projects and match it to standardized parameters to categorize the NIH research projects. The public can access the resulting categorical spending reports on the RePORT website.

NIH developed RCDC because it needed a more consistent system for reporting on its research spending and saw that advances in computer technology for data and text mining would enable the agency to modernize its systems. About the same time, the National Academies, an organization that provides scientific advice to the Federal government, issued two reports recommending a change in the way NIH categorizes its research portfolio. Subsequently, the U.S. Congress, through the NIH Reform Act of 2006,[23] mandated that NIH build a tool to categorize the agency's research.

Hundreds of NIH technical and scientific experts helped create the RCDC categorization methods and identify key terms and concepts. RCDC provides increased consistency of reporting, and in turn, enhances NIH's capacity for portfolio analysis and strategic planning. RCDC also provides improved transparency through the RePORTER database, and improves NIH's accountability for its spending and ability to respond to public inquiries.

The 215 categories reported through the RCDC process are the same categories that historically have been requested by and reported to Congress and the public at the end of each fiscal year. Some of the research funding amounts that the RCDC system reports may differ from NIH reports issued in the past. That is because the RCDC process applies a uniform definition, for each category, across all NIH's research projects. Individual research projects can be included in multiple categories, so the sum of all research/disease categories does not add up to 100 percent of NIH-funded research for a given fiscal year. The annual estimates reflect amounts that change as a result of science, actual research projects funded, and the NIH budget. Despite the changes in categorizing NIH research using the RCDC system, NIH's methods for budgeting and spending tax dollars remain the same.

RePORTER: Expanded Information on Scientific Projects

For many years, one of the most common ways for the public to find information on NIH research programs was to search for projects in NIH's Computer Retrieval of Information on Scientific Projects (CRISP) system. Now a new system that provides much more detailed information about projects is on-line. The new system, accessed through the RePORT website, is called RePORTER (RePORT Expenditures and Results). Like its predecessor CRISP, RePORTER allows users to locate and view NIH awards using their own search criteria. However, RePORTER also gives users access to budget award information, research results, and other research outcomes such as patents and publications. RePORTER includes data from 1985 through to the present—including projects funded through ARRA—and project lists can be sorted and downloaded to Excel. New features will continue to be added to RePORTER in several releases throughout FY 2010.

[22] New Investigators lack previous, major NIH funding. Early Stage Investigators are New Investigators within 10 years of completing their terminal degrees or residencies.
[23] NIH Reform Act of 2006, Pub. L. No. 109-482, Sec. 402B.

Capitalizing on Discovery

Technology Transfer

Technology transfer is essential to ensuring that the public has ongoing access to new and more effective health care products and procedures resulting from advances in medical research. 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 entity best suited to conduct the further research and development needed for potential commercialization and public health benefit. HHS has designated NIH as the lead agency for biomedical technology transfer and intellectual property (IP) policy matters affecting public health. The NIH Office of Technology Transfer (OTT) evaluates, protects, markets, licenses, monitors, and manages the wide range of intramural NIH and FDA discoveries and inventions; works with NIH's Office of Financial Management to manage the NIH Royalties Program; and takes the lead in developing technology transfer policies for NIH's intramural and extramural research programs.

Technology transfer policies, as they apply to extramural research, are administered by NIH OER and include principles, guidelines, and regulations related to invention reporting and intellectual property policy matters. NIH extramural policies are designed to enhance access to publications resulting from NIH-funded research (see *NIH Public Access Policy* below in this chapter); 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 OER administers the web-based Interagency "Edison" (iEdison) electronic reporting system through which inventions supported by more than 20 Federal research agencies can be reported through a single interface; approximately 500 grantee or contractor organizations are registered and using the system.

For the intramural research program, OTT reviews invention disclosures reported by the ICs and FDA; works with ICs/FDA to assess commercial and patent potential; oversees patent prosecution; negotiates licenses for commercial use in research and development; monitors licensing agreements with companies to ensure development compliance and royalty payment obligations; and administers the collection and distribution of royalties. Over the past decades, NIH has executed thousands of license agreements. In calendar year 2009, licensees reported nearly $6 billion in sales of products covered by NIH licenses (see Table 2).

Table 1-2: Intramural Technology Transfer this Biennial

Activity	FY 2008	FY 2009
New U.S. patent applications filed	176	156
Patents Issued	88	110
Licenses Executed	259	215
Royalties Earned	$ 97,200,000	$91,200,000

NIH technology transfer activities include marketing and outreach to companies, coordinating inter- and intra-agency activities, and facilitating access to patented technology for NIH intramural and extramural research programs. The NIH Pipeline to Partnerships (P2P) searchable database, developed with the NIH Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) programs, encourages the development of technologies licensed from

OTT or being developed by NIH SBIR/STTR awardees. P2P has expanded to include unique technologies from 158 companies as of November 2009. OTT also has launched the electronic Product Showcase to display technologies from NIH intramural research that were licensed to companies for commercial development and now are on the market. These products are used every day to detect, treat, or prevent disease or assist researchers as tools to explore ways to develop newer and more effective health care products and procedures. As of November 2009, there were 225 products in the Showcase database with new ones added regularly.

The National Library of Medicine

Through NLM, NIH provides the world's largest medical library, including electronic information services that deliver trillions of bytes of data to millions of users every day. The library collects materials in all areas of biomedicine and health care and plays a pivotal role in translating biomedical and behavioral research into practice. NLM collections stand at more than 12 million items—books, journals, technical reports, manuscripts, microfilms, photographs, and other forms of medical information. To maintain the currency of its collection, the library acquires publications from a wide variety of sources. Each year NLM reviews and processes approximately 25,000 monographic items for possible addition to the NLM collections, and acquires and licenses more than 22,000 print and electronic serial titles. 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, NLM also is responsible for PubMed®/MEDLINE®, a database freely accessible on the Internet and that has more than 19 million journal article references and abstracts going back to 1948. The database draws on 5,300 of the world's leading biomedical journals published in the United States and more than 80 other countries. Links from PubMed references to full text articles in PubMed Central, NLM's digital archive of journal articles, or on publisher websites are now available for more than half of the 19 million references—and more than 86 percent of those published after 1999. MedlinePlus, a companion Web information service, is a goldmine of authoritative, up-to-date health information from all NIH components, other Federal agencies, and authoritative private organizations. It includes information about prescription and over-the-counter drugs, an illustrated medical encyclopedia, interactive patient tutorials, and the latest health news for health professionals and consumers alike, and gives easy access to medical journal articles. In FY 2008, high-quality consumer health information in more than 40 languages (beyond English and Spanish) was added to MedlinePlus to address the growing need for understandable information for non-English-speaking patients treated in hospitals and clinics across the United States. More than three billion searches of NLM online information resources are done each year by health professionals, scientists, librarians, and the public. (See also the sections on *Disease Registries, Databases, and Biomedical Information Systems* and on *Health Communication and Information Campaigns and Clearinghouses* in Chapter 3).

To manage its collection and maximize accessibility, NLM 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 descriptors in a hierarchical structure that permit searching at various levels of specificity. The MeSH® thesaurus is used for indexing articles for PubMed/MEDLINE.

The library virtually stands at the center of biomedical research—receiving, storing, disseminating, and connecting published research results, including articles deposited in response to the NIH Public Access Policy (see section below), with research data from laboratories and research centers around the world. NLM also supports, develops, and disseminates standard medical terminologies in the Unified Medical Language System. As the HHS coordinating body for clinical terminologies, NLM plays a leadership role in developing U.S. and international health data standards, including those related to electronic health records and the expansion of standards to cover genetic tests.

Public Access Policy

The NIH Public Access Policy ensures that the published peer-reviewed results of NIH-funded research are accessible to the public. In April 2008, the NIH mandatory Public Access Policy regarding peer-reviewed publications took effect. This policy replaced a voluntary practice that had been in place since May 2005. In accordance with the Consolidated Appropriations Act of 2008[24] and the Omnibus Appropriations Act of 2009,[25] the NIH Public Access Policy now requires the submission of peer-reviewed papers resulting from NIH-funded research to PubMed Central (PMC), a free, full-text, digital archive of biomedical, behavioral, and life sciences journal literature. These papers are made publicly available on PMC within 12 months of the official publication date. PMC and its international sites in the United Kingdom and Canada also support the public access policies of other U.S. and international funders of biomedical research.

The NIH Public Access Policy is off to a promising start, and NIH has made considerable progress toward full compliance. During the voluntary period (May 5, 2005, to December 31, 2007), NIH was able to collect only 19 percent of the target estimate of 80,000 papers per year arising from NIH funds. Based on publication data for July 2008 to June 2009, it is estimated that NIH now funds approximately 88,000 papers a year. Even with the higher target, NIH has received more than 60 percent of the papers published between July 2008 and October 2009.[26] These papers either are already available in PubMed Central or will be at the expiration of the typical 12-month embargo. This positive beginning to the requirement is due in large part to cooperation from NIH awardees and publishers. Since the policy became a requirement, the percentage of final published papers deposited directly by publishers has increased from 12 to 26 percent, and manuscripts submitted by authors have increased from 7 to 36 percent.

Through the Public Access Policy, NIH has been able to make tens of thousands of papers publicly available on PMC, which contains more than 1.9 million papers overall, most from publishers who have been participating in PMC since 2000. These papers are heavily accessed. On an average weekday, some 360,000 users retrieve more than 700,000 papers. These users include patients, doctors, educators, and scientists at universities and small businesses. Access to NIH-supported papers on PMC increases the likelihood that all of these groups will use the NIH investment in research to improve public health.

[24] Division G, Title II, Section 218 of Pub. L. No. 110-161.
[25] Division F Section 217 of Pub. L. No. 111-8.
[26] The period from January 2008 to June 2008 is not reported, as papers published during these months were likely accepted for publication after the law creating the policy change was passed, but before the policy requirement took effect, and their rates are therefore possible to attribute to either policy condition.

Ensuring Responsible Research

NIH recognizes that with public support for research comes an obligation to ensure that research is conducted in a responsible manner to promote the integrity of NIH-supported biomedical and behavioral research and research training, to protect the health and safety of the public, and to conserve public funds. Responsible conduct of research features many interrelated attributes—including objectivity, honesty, accuracy, efficiency, safety, and ethical behavior. NIH addresses these issues through an array of policies, programs, and activities.

Ethical Conduct

Ethical Conduct for NIH Employees

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 meet that responsibility. The Ethics in Government Act (5 U.S.C. Appendix) requires each agency to provide an initial ethics orientation to new employees. NIH provides a Web-based training system to meet that obligation, as well as the annual ethics training for all other NIH staff. It is significant to note that, since 2004, NIH has made annual ethics training mandatory for all employees, a standard that far exceeds the government-wide requirement.

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. NIH ethics staff members are readily available to answer questions and provide ethics and conflict-of-interest counsel, as needed, and the NIH Ethics Office provides extensive information and resources on its website. 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. For the ethics staff, there are semi-monthly meetings and extensive NIH Ethics Office-sponsored training in selected topics throughout the year. Training opportunities from the Office of Government Ethics also are made available to NIH ethics staff and are-well attended.

Financial Conflict of Interest in Extramural Research

Proper stewardship of Federal funds includes ensuring objectivity of results by protecting federally funded research from compromise by financial conflicts of interest (COIs). Public Health Service (PHS) and HHS regulations (42 CFR 50, Subpart F, and 42 CFR 94), promote objectivity in NIH-funded research by providing standards to ensure that the design, conduct, and reporting of research under NIH-funded awards is not biased by any financial COI. The regulations are applicable to institutions that apply for PHS[27] funding for research and, through implementation of the regulations by these institutions, to each investigator participating in the research. Each institution receiving NIH research funds is required to have written guidelines on the avoidance of COI (i.e., financial interests, gifts, gratuities and favors, nepotism, and other areas such as political participation and bribery) and on the management, reduction, and elimination of identified conflicts. Institutions are required to report identified investigator financial COIs to the Grants Management Officer at the funding IC.

The regulations that govern objectivity in research were established in 1995. In the intervening years, the pace of translation of discoveries into interventions has accelerated significantly. Also, the U.S. biomedical research enterprise has grown in size and complexity. Awareness of the increasing complexity of biomedical research and the increased interaction between the government and the private sector in meeting common public health goals led to the question of whether changes to the regulations are needed. NIH recognizes that improvements can be made to its system of oversight,

as well as to recipient organizations' management of the financial COI process, but also believes that the complex and controversial issues surrounding financial COI warrant a carefully considered, open dialogue with all affected parties. For these reasons, NIH, on behalf of HHS and PHS, developed an Advanced Notice of Proposed Rulemaking (ANPRM) to begin a dialogue about broadening the regulations to address institutional COI and to gain public input on all aspects of potential regulation in this area.

The comment period for the ANPRM closed on July 7, 2009. NIH is analyzing the comments received, as well as other related information, to determine how best to move forward in potentially changing the current regulations. If regulatory change is deemed appropriate, a Notice of Proposed Rulemaking would allow for further public comment on any draft regulation. If warranted, the goal would be to have new regulations announced with initial implementation by fall 2010.

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

Conflicts of Interest in Clinical Research

COI can be especially problematic in clinical research. For that reason, there is guidance in addition to the policies and regulations noted above. The OHRP guidance, "Financial Relationships and Interests in Research Involving Human Subjects," covers extramural research and the NIH "Guide to Preventing Financial and Non-Financial Conflicts of Interest in Human Subjects Research at NIH" ensures both the integrity of research and the safety of subjects in the intramural program.

Research Integrity

NIH recognizes that public support for research comes with an obligation to promote integrity in the conduct of that research. Honesty, accuracy, efficiency, and objectivity are important values that characterize what is meant by integrity in research. As defined by regulation,[28] *research misconduct* means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results; it does not include honest error or differences of opinion. Allegations of research misconduct in biomedical and behavioral research or research training supported by NIH tend to be unique rather than routine events at most institutions. However, a research misconduct allegation has the potential for high impact on public health or clinical treatment, the individuals involved, the institution where the alleged misconduct took place, and public trust. (See also, *Ethical Conduct*, above).

OER manages allegations of potential research misconduct that are reported to any member of the NIH extramural staff, and also provides annual training to the IC Research Integrity Officers (RIOs) and extramural staff, through online tutorials and training symposia. Within each IC, a senior official is designated as the IC RIO. Extramural staff is instructed to report immediately any allegation of potential research misconduct to the IC RIO, who then forwards the allegation to one of the Extramural Research Integrity Liaison Officers or the Agency Extramural Research Integrity Officer in OER. A preliminary review of the allegation is conducted then to verify information and assess whether the allegation may be appropriate for an inquiry. On rare occasions, NIH may request an inquiry, but by regulation, the HHS Office of Research Integrity is authorized to request institutions to perform inquiries and investigations related to allegations of potential research misconduct. If a finding of research misconduct is found, the offender may incur administrative actions, including but not limited to: replacement as Principal Investigator on the award; requirement to clarify, correct, or withdraw related publications; suspension or termination of any PHS grant, contract, or cooperative agreement; ban from serving in any advisory capacity to PHS; and suspension or debarment, i.e., exclusion from eligibility for Federal grants, contracts, and cooperative agreements.

The same standards of research integrity and comparable procedures for investigating allegations of scientific misconduct apply to NIH intramural research program. For intramural research staff, the "Guidelines for the Conduct of Research" set forth the general principles governing the conduct of good science. The guidelines cover the responsibilities of research staff in the collection and recording of data, publication practices, authorship determination, mentoring, peer review, confidentiality of information, collaborations, and financial conflicts of interest. NIH employees are required to report suspected or apparent misconduct in science to the Agency Intramural Research Integrity Officer (AIRIO) or Deputy Director for Intramural Research. The AIRIO decides whether the allegation warrants an inquiry to determine whether there is enough evidence behind an allegation or apparent instance of scientific misconduct to warrant moving to the next level of response—an investigation. If the formal investigation determines that misconduct has occurred, NIH sanctions could include removal from a particular project, special monitoring of work, suspension without pay, or termination of employment. The NIH AIRLO decides whether to accept the investigation report, makes a finding of misconduct, and imposes the recommended NIH sanctions. The final step in the process is a review by the HHS Office of Research Integrity, which then makes recommendations on possible PHS sanctions that could include debarment from serving on NIH study sections or receiving NIH grants. The *Intramural Research Program Sourcebook* contains all Policies and Procedures for Investigating Scientific Misconduct.

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, (4) providing educational materials and programs for investigators and IRBs, and (5) overseeing compliance. Because of the clinical research conducted in the NIH intramural program, NIH itself has an assurance with OHRP. (See also, *Ethical Conduct*, above for information on OHRP guidance concerning COI in human subject research).

The Office of Extramural Programs (OEP) in the NIH OER conducts activities to ensure the compliance of NIH grantees with HHS regulations and NIH policies regarding the protection of human subjects in extramural research. OEP staff assess the proposed resolution of human subjects concerns identified during peer review of extramural research applications prior to funding, and respond to requests to change human subjects designations of ongoing NIH extramural research projects. OEP also provides training to NIH extramural staff and the extramural scientific community regarding NIH policies on human subject protection and develops and implements policies to ensure that participants in NIH-funded extramural research projects are adequately protected. OER maintains a grants policy website dedicated to research involving human subjects. This comprehensive site provides, in one place, HHS and NIH requirements and resources for the extramural community involved in human subjects research in its roles as applicants/grantees, offerors/contractors, peer reviewers, and institutional officials.

As noted above, because of the clinical research conducted in the NIH intramural program, NIH itself has an OHRP-approved Federal-Wide Assurance (FWA) of compliance with the HHS regulations for the protection of human subjects. The Office of Human Subjects Research (OHSR) in the NIH OIR—functioning under the assurance and in cooperation with the ICs—implements the policies and procedures of the NIH Human Research Protection Program. With the responsibility to protect the rights and safeguard the welfare of human subjects who participate in intramural NIH research studies, OHSR establishes and maintains the 11 NIH IRBs that are linked to the FWA, provides training for researchers and IRB members, and manages the Human Subjects Research Advisory Committee. In turn, the 11 NIH IRBs are responsible for the prospective and continuing review of NIH intramural research that involves human subjects. The Human Subjects Research Advisory Committee advises the DDIR on policies and procedures regarding the conduct of human subjects research. The importance of this advisory role is underscored by the fact that, under the FWA, the DDIR is the institutional official responsible for human subject investigations at NIH. An additional body, the NIH Intramural

Clinical Research Steering Committee, also serves as a forum for trans-NIH governance and policy development in the area of human subjects research. The Committee coordinates efforts and ensures clear communications about goals, progress, and future directions. 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, and is available as a source of advice to the NIH IRBs.

NIH also is working to enhance the safety, efficiency, and effectiveness of the clinical research enterprise by promoting greater consistency in the rules and policies governing the conduct and oversight of clinical research. In addition to the regulations administered by OHRP, clinical investigators are subject to FDA regulations. Moreover, differences in the HHS and FDA regulations can be compounded through policy interpretation. In addition, policies and practices of the NIH ICs can lead to other complications for clinical investigators supported by NIH. Recognizing that the inconsistencies in the oversight system can hamper the efficiency and effectiveness of the clinical research system, NIH created the Clinical Research Policy Analysis and Coordination (CRpac) Program to promote greater consistency in human subject protection policies and requirements. Launched as an NIH Roadmap initiative, CRpac aims to advance the development of clear, effective, and coordinated rules for clinical research to achieve maximally effective human subject protections. For example, CRpac has led major efforts to improve understanding and compliance with adverse event reporting requirements and standardize the reporting of adverse event data,[29] and to develop draft guidelines for human specimen and data collections funded by NIH. (See also the section on *Clinical and Translational Research* in Chapter 3.)

Animal Care and Use in Research

The Office of Laboratory Animal Welfare (OLAW) in the NIH OER oversees the use of animals in NIH-supported biomedical and behavioral research conducted by extramural institutions. OLAW provides guidance and interpretation of the *PHS Policy on Humane Care and Use of Laboratory Animals*; monitors compliance with the policy; evaluates all allegations or indications of noncompliance with Federal animal welfare requirements; 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, and committing the institution and its personnel to full compliance. OLAW negotiates and approves these assurances as required by Pub. L. No. 99-158, HHS acquisition regulations, and the PHS policy, and holds institutional officials, Institutional Animal Care and Use Committees (IACUC), researchers, and other agents of the institution accountable for ensuring conformance with the institution's Assurance.

OLAW maintains a comprehensive website 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 2008, two online seminar series were launched to focus educational outreach to institutional officials at grantee institutions and to IACUC members. The webinar format enabled invited speakers to communicate timely, relevant information through an interactive forum with constituents at worksites across the Nation, at no expense to the viewers. The feedback on the seminars has been extremely positive, and the process has been fine-tuned to enhance the experience and extend the number of attendees to more than 300 institutions.

A workgroup led by OER developed a new comprehensive Animals in Research website in 2008. The website provides information for the general public about the benefits of medical research with animals, alternatives to animal research, advances in animal research, and animal health and welfare. For researchers and institutions, the website provides information about emergency preparedness and crisis communication, up-to-the-minute policy and guidance, grants resources, funding opportunities, and training and education, as well as answers to frequently asked questions.

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, which reviews and approves (or disapproves) requests to use animals in research, and has a senior veterinarian who directs its animal care and use program. An Animal Research Advisory Committee meets monthly to discuss trans-NIH topics and provide advice to the NIH DDIR, 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.

Bioethics Research, Training, and Translation

NIH has a long history of engagement with bioethics—the study of ethical issues and controversies resulting from advances in biology and medicine. NIH was a pioneer in the development of independent ethical review of clinical research studies. In 1996, NIH established the Department of Bioethics within the NIH Clinical Center to conduct conceptual, empirical, and policy-related research into bioethical issues; offer training and educational programs in bioethics; and provide ethics consultation to clinicians, patients, and families. In the 1990s, NIH began a dedicated investment in the study of the ethical, legal, and social implications of genome research through a novel set-aside, as part of the Human Genome Project. And, in the last two decades, NIH has supported many additional bioethics research and training projects, ranging from short-term courses in research ethics regarding minority participation in AIDS research to studies addressing the ethical, social, and legal issues of human microbiome research. Nonetheless, advances in science and medicine have been accelerating at a rapid pace and, more than ever, NIH needs the foresight and vision to understand the ethical and societal implications of discoveries in biomedical, behavioral, and technological research and the knowledge arising from these advances. In the last 3 years, there also have been calls for NIH to make a greater and wider commitment to addressing the ethical, legal, and social issues—such as, privacy, safety, commercialization, and COI—raised by the research it supports—including biotechnology, tissue engineering, nanomedicine, and synthetic biology. NIH's commitment to the support of bioethics helps maintain and enhance public trust and confidence as NIH explores new frontiers in science.

Integrating bioethics across the entire NIH research portfolio is a long-range agency goal that requires mid- and long-term planning and strategies. As a first step, a trans-NIH task force was formed in early 2009 to develop a research agenda for FY 2010 and FY 2011 and to develop a long-range plan. Additional support for bioethics research was provided through the FY 2009 ARRA Challenge Grant initiative. Support also has been requested in FY 2010 through NIH's regular appropriations process.

The long-range plan will identify research and training gaps and opportunities and formulate a strategy for addressing them over the next 5 to 10 years. It also will include consideration of the optimal administrative approach for sustained support for, coordination of, and accountability for NIH bioethics efforts. Finally, the long-range plan will include the design of an evaluation to assess the value and impact of the investments. Altogether, the plan will provide a framework that will enhance the integration of ethical inquiry and practice into the conduct of research across the entire spectrum, from the most basic projects to the most applied; help maintain the academic discipline of bioethics and expand bioethics investigators and scholars; and develop curricula and ethics training programs. The goal is to facilitate the early identification and deliberation of complex bioethical issues and generate knowledge needed for responsible conduct of science that takes into account its broader societal impact.

Promoting Responsible Research through Policy Development

NIH has a vested interest in promoting research at the cutting edge of science and technology—for example, gene transfer, infectious agents, stem cells, nanomedicine—research that has potential benefits but often unknown risks for which little or no guidance exits. For example, the protection and enhancement of public health, agriculture, and the food supply is a national priority and has led to increased Federal funding for research on infectious agents, especially those that pose a severe threat to human, plant, and animal health. At the same time, concerns have been voiced by the public, scientific community, Administration, and Congress regarding biosafety and biosecurity in research laboratories that work with the

most dangerous pathogens and toxins. Concerns also have been raised about the risks that certain information from life sciences research could be misused to threaten public health and other aspects of national security. NIH has a responsibility to anticipate the evolution of issues such as these, and to provide leadership and support for efforts at the NIH, HHS, and national levels that are designed to promote research, assure safety, address ethical concerns, and enhance public understanding and trust, through the development of sound public policies.

Much of the leadership and support regarding new and evolving policies about responsible conduct of research is vested in the NIH Office of Science Policy (OSP). Within OSP, the Office of Science Policy Analysis (OSPA) coordinates NIH responsibility for the interpretation, development, and implementation of policies regarding human embryonic stem cells. In addition, OSPA coordinates action on nanotechnology policy issues. This includes providing management and analytic support for the Trans-NIH Nanotechnology Task Force. The Office of Biotechnology Activities (OBA), also within OSP, monitors scientific research and progress in the areas of recombinant DNA,[30] genetics technologies, and dual-use research[31] to anticipate future developments, including potential safety, ethical, legal, and social concerns. OBA also manages the CRpac program, discussed above, which promotes greater consistency in human subject protection policies and requirements.

Stem Cell Research

NIH is responsible for the interpretation and implementation of legislation, Executive Orders, and Administration policies relating to stem cell research. OSPA advises NIH, Congress, the scientific community, and the public on current stem cell policies and specific research activities allowable under current policies and regulations. The office plays an integral role in developing guidelines for research involving human pluripotent cells of all types.

On March 9, 2009, President Barack Obama issued Executive Order 13505: *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells*. The Executive Order states that the Secretary of HHS, through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law.

The NIH Guidelines for Human Stem Cell Research were published on July 7, 2009, and are available at http://stemcells.nih.gov/policy/2009guidelines.htm. The Guidelines implement the Executive Order as it pertains to extramural NIH-funded stem cell research, establish policy and procedures under which the NIH will fund such research, and help ensure that NIH-funded research in this area is ethically responsible, scientifically worthy, and conducted in accordance with applicable law. In addition, on July 30, 2009, the President directed all Federal departments and agencies that support and conduct stem cell research to adopt the Guidelines. For hESCs derived from embryos donated in the United States on or after the effective date of the Guidelines (July 7, 2009), specific provisions regarding the embryo donation and informed consent process apply and are detailed in Section II of the Guidelines.

On September 21, 2009, NIH Director Francis S. Collins announced that NIH is accepting requests for human embryonic stem cell lines to be approved for use in NIH-funded research. Dr. Collins also announced the members of a new working group of the Advisory Committee to the Director (ACD)—the Working Group for Human Embryonic Stem Cell Eligibility Review. After considering the analysis done by the Working Group, the ACD makes recommendations to the NIH Director regarding the eligibility of particular human embryonic stem cell lines for use in NIH-funded research. hESCs that meet Section IIA requirements are considered through NIH administrative review.

The NIH Director makes the final decisions regarding the eligibility of all hESCs. Those lines deemed eligible are listed on the NIH Human Embryonic Stem Cell Registry. Once a human embryonic stem cell line is listed on the Registry, there is no need for further submissions requesting review of that particular line. The first hESCs were listed on the Registry on December 2, 2009.

Recombinant DNA, Genetic Technologies, and Dual-Use Research

OBA manages a range of activities related to responsible use of recombinant DNA, genetic technologies, and dual use research including:

- Administration of the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines*), which address the safe and ethical use of basic and clinical research involving recombinant DNA molecules at institutions that receive any NIH funding for recombinant DNA research;
- Management and analytical support for the NIH Recombinant DNA Advisory Committee (RAC);
- Operation of the NIH Genetic Modification Clinical Research Information System (GeMCRIS), an electronic resource for information and adverse event reporting on gene transfer trials, which also is used by FDA;
- Outreach and education to stakeholder communities regarding biosafety and biosecurity; and
- Management and analytic support for the National Science Advisory Board for Biosecurity (NSABB).

The RAC reviews all proposals for human, gene transfer, and 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, enabling 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 RAC website to enhance their accessibility to the scientific and lay publics. As new issues are identified, the RAC helps NIH develop safety symposia and policy conferences to engage the scientific and public communities in thoughtful dialogue regarding emerging issues and concerns.

The 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. For example, in March 2009, NIH published in the *Federal Register* a proposal for comment to expand the scope of the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines*) to include nucleic acid molecules that are synthesized rather than being made by recombinant techniques. The proposal represents the first major expansion to the document's scope since it was first written more than 30 years ago. This action was in response to a recommendation made in the December 2006 report of NSABB, *Addressing the Biosecurity Concerns Related to the Synthesis of Select Agents*. NSABB recommended to the HHS Secretary that the language and implementation of current biosafety guidelines be examined to ensure that such guidelines and regulation provide adequate guidance for working with synthetically derived nucleic acids. NIH was tasked with conducting the assessment. OBA also consulted with the RAC, which noted that the biosafety risks are related more to the product being produced than the technique being used, and recommended expanding the scope of the *NIH Guidelines* to specifically cover synthetic nucleic acids. The public comments generally have been supportive of the proposal. NIH also held a public consultation about the proposed changes in a day-long meeting in June 2009. A revised version of the proposal was reviewed by the RAC at its quarterly meeting in December 2009. A *Federal Register* notice requesting comment on a revised proposal was published on April 22, 2010. OBA anticipates a final proposal will be published by the end of 2010.

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. SACGHS is charged with undertaking 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 April 2008, SACGHS submitted its report on the *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*. The report is the culmination of extensive fact finding, analysis, expert consultation, outreach to the public, and deliberation by the committee, and highlights gaps in the oversight system for genetic testing and provides recommendations to maximize the benefits of genetic testing and minimize harms.

OBA also is a focal point for the development of policies addressing biosafety and biosecurity. This includes the development of policy regarding dual use research (life sciences research that yields information or technologies with the potential to be misused to threaten public health or endanger other aspects of national security). NIH was a key participant

in the HHS Trans-Federal Task Force on Optimizing Biosafety and Biocontainment Oversight, which was established in FY 2008 in response to concerns about the risks associated with the proliferation of high- and maximum-containment laboratories in the United States. The Task Force reviewed the current systems of biosafety oversight and made recommendations to improve biosafety and biocontainment oversight at U.S. laboratories. NIH also participated in the Working Group on Strengthening Laboratory Biosecurity in the United States, established in January 2009, by Executive Order 13486, *Strengthening Laboratory and Biosecurity in the United States*. The Working Group is charged with reviewing and evaluating laboratory operations regarding the use, handling, storage, or transport of biological Select Agents and toxins.[32] The Working Group developed a report, which included recommendations for new legislation, regulations, guidance, and practices for enhancing laboratory security and reliability of personnel at all Federal and nonfederal facilities working with biological Select Agents and toxins. NIH also has developed new, comprehensive biosafety recommendations for work with potentially pandemic flu viruses[33] that have the ability to infect humans. The guidance was developed to ensure that important research on pandemic influenza is carried out using biosafety containment and practices that will protect laboratory workers and the public.

NSABB, managed by OBA, is a Federal advisory committee established to advise the Federal Government on ways to minimize dual use biological research risks and inform the development of Federal and institutional oversight guidelines. In response to heightened security concerns surrounding the potential misuse of dangerous pathogens within research settings, NSABB was charged with recommending strategies for enhancing the reliability of personnel who have access to Select Agents and toxins. The challenge was to identify policies aimed at mitigating the risk of misuse of Select Agents by individuals who have legitimate access to them as part of their jobs, without unduly hindering the pace of life sciences research. The NSABB issued its findings and recommendations in May 2009, and they are being considered at various levels of the Federal Government, along with those of the Executive Order Working Group and other groups that have focused attention on these important issues.

[27] The PHS comprises all HHS Agency Divisions (of which NIH is 1 of 11) and the Commissioned Corps.
[28] 42 CFR Parts 50 and 93. Available at: http://ori.dhhs.gov/documents/42_cfr_parts_50_and_93_2005.pdf.
[29] An adverse event is an unfavorable medical occurrence associated with the subject's participation in research.
[30] Recombinant DNA is DNA created by combining genetic material from different sources to create a new genetic sequence.
[31] Dual-use research is defined as biological research with legitimate scientific purpose that may be misused to pose a biologic threat to public health and/or national security.
[32] Select Agents are biological agents and toxins that have the potential to pose a severe threat to public, animal or plant health, or to animal or plant products. The possession, use, and transfer of Select Agents and toxins are regulated by HHS and the U.S. Department of Agriculture.
[33] Examples include 1918 H1N1, human H2N2 that circulated in 1957-68, and strains of HPAI H5N1.

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2 SUMMARY OF RESEARCH ACTIVITES BY DISEASE CATEGORY

Biennial Report of the Director

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Volume II

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An electronic version of this report is available at: http://biennialreport.nih.gov and contains many live links to NIH programs, plans, and publications.

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Cancer

Cancer research continues to move toward a new era of personalized medicine. Cancer is not a single disease, but a complex of diseases in which genetic changes disrupt molecular pathways. Patients with identical diagnoses may experience different symptoms, different responses to the same treatment, and ultimately different outcomes. A better understanding of the genetic glitches that cause the various diseases we call cancer can open the door for targeted treatment for each individual and enable more predictive and individualized approach to care. The recent identification of genetic mutations linked to breast, colorectal, and many other cancers has demonstrated the value and feasibility of pursuing more comprehensive knowledge of the molecular origins of cancer. In 2006, NIH initiated a pilot project designed to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies. Three years later, The Cancer Genome Atlas (TCGA) has identified many of the major genomic changes in hundreds of brain and ovarian tumors. Specifically, TCGA first characterized glioblastoma—an extremely deadly form of cancer—and revealed at least three genes involved in these tumors and four distinct subtypes. Importantly, the data generated are a community resource and thus made available in the public domain days after being produced by the research network. With that foundation of success, TCGA now is expanding to identify all of the relevant genomic alterations in 20 major tumor types in hopes of continuing this model of enabling the next generation of discovery that promises to improve cancer diagnosis, prevention, and care.

Introduction

Cancer—a leading cause of death among Americans, accounting for more than 560,000 deaths in 2007—is not a single disease. More than 100 types of cancer have been identified based on their association with different organs and cell types. However, within each type of cancer an individual's tumor can differ greatly due to complex biological factors. Cancer arises from alterations in the interactions among layered biological systems. The many different forms of cancer can be understood only by characterizing these systems and how they interact. NIH cancer research programs aim to improve our understanding of cancer as a multiscale, multidimensional disease system. This approach provides a context for research on: preventing cancer through risk assessment based on genetic susceptibilities and environmental exposures; detecting and diagnosing cancer based on knowledge of cancer signaling pathways and biomarkers; predicting cancer progression and outcomes based on examination of the tumor microenvironment and interactions between tumor cells and surrounding, noncancerous cells; developing personalized interventions for individual cancer patients based on predictions of their response to treatment; and addressing the unique needs of the growing number of cancer survivors.

To take full advantage of the scientific opportunities in cancer research, including the opportunities generated by the convergence of emerging technologies with advances in molecular sciences, an action plan has been created to ensure that the use of these new funds is optimally leveraged to understand and control cancer. *The NIH Strategic Plan to Double the NIH Cancer Research Budget* focuses on understanding the causes and mechanisms of cancer; accelerating progress in cancer prevention; improving early detection and diagnosis; developing effective and efficient treatments; understanding factors that influence cancer outcomes; improving the quality of cancer care; improving the quality of life for cancer patients, survivors, and their families; and overcoming cancer health disparities. Using cancer as a model that could inform basic biology and physiology of all diseases, NIH has developed a blueprint for 21st-century personalized medicine. This new investment plan extends the scope of cancer research to embrace scientists and clinicians working on other diseases who heretofore may not have been members of the oncology research community.

NIH has identified seven objectives related to cancer research to be supported with ARRA funds: (1) accelerating and expanding cancer research; (2) advancing personalized cancer treatment and prevention; (3) redesigning the cancer research bioinformatics infrastructure; (4) revamping the cancer clinical trials system; (5) fostering collaboration to increase the impact of cancer research; (6) strengthening the research workforce; and (7) improving care and quality of life

for all cancer patients. NIH will use ARRA funds to support three signature cancer-related initiatives to accelerate cancer research and advance personalized medicine: the Cancer Genome Atlas (to support development of targeted prevention, detection, and treatment methods), the Physical Sciences-Oncology Centers Program (to improve understanding of cancer's causal pathways), and the Personalized Cancer Care/Drug Development Platform (to support development of individually tailored interventions).

As the NIH vision of personalized medicine evolves, doctors will be able to use detailed information about an individual's cancer and employ molecular and clinical data to guide the selection of therapies or preventive measures that are most likely to be safe and effective for that person. Personalized medicine promises to improve quality of life for cancer survivors, minimize adverse side effects of therapy, and reduce disparities among populations currently experiencing an excess burden of cancer.

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Cancer research is conducted by a number of ICs; however, most of the research investment is committed to NCI programs. Five NCI extramural divisions support research carried out at nearly 650 universities, hospitals, cancer centers, specialized networks and research consortia, and other sites throughout the United States and in more than 20 other countries. In addition, NCI provides infrastructure to help the greater cancer research community take advantage of the potential benefits of emerging technologies (e.g., genomics, proteomics, bioinformatics, and molecular imaging). NCI's two intramural divisions conduct basic, translational, clinical, and population research, making fundamental discoveries related to cancer causes and mechanisms, genetics, and host immunological and other responses to cancer and aim to rapidly translate those findings into novel preventive and detection methods and therapies.

Cancer research conducted or supported by other NIH ICs is wide-ranging and often coordinated with NCI programs and grantees—for example, the Surveillance, Epidemiology, and End Results (SEER) program (a source of information on cancer incidence and survival in the United States) and the nationwide network of Comprehensive Cancer Centers. Examples of cancer research within other ICs include:

- Fogarty International Center for Advanced Study in the Health Sciences (FIC): international studies and collaborations on cancer research
- National Eye Institute (NEI): research on cancers of the eye
- National Heart, Lung, and Blood Institute (NHLBI): research on blood-related cancers and support for breast, colorectal, and reproductive cancer as the administrative coordinator of the NIH Women's Health Initiative
- National Center for Complementary and Alternative Medicine (NCCAM): research on nontraditional approaches to cancer therapies across the cancer continuum
- National Human Genome Research Institute (NHGRI): epidemiological and genomic research on cancers
- National Center on Minority Health and Health Disparities (NCMHD): research on cancer in diverse populations
- National Institute on Aging (NIA): research on prostate and skin cancers and the biology of aging as it relates to cancer
- National Institute on Alcohol Abuse and Alcoholism (NIAAA): research on the role of alcohol in colorectal, breast, liver, and pancreatic cancers
- National Institute of Allergy and Infectious Diseases (NIAID): technology development in support of cancer research, diagnosis, and therapy and studies of the role of viruses in cancer
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS): research on skin and bone cancers
- National Institute of Biomedical Imaging and Bioengineering (NIBIB): imaging and bioinformatics technology development in areas that are vital to cancer research
- National Institute of Child Health and Human Development (NICHD): research on breast and reproductive cancers
- National Institute on Drug Abuse (NIDA): research on treatments for tobacco addiction serving as cancer prevention

- National Institute on Deafness and Other Communication Disorders (NIDCD): research on deafness and communication disorders in relation to head and neck cancers
- National Institute of Dental and Craniofacial Research (NIDCR): research on head and neck cancers
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): research on liver, prostate, kidney, colorectal, and bladder diseases and conditions that may lead to cancer
- National Institute of Environmental Health Sciences (NIEHS): research on the effects of biological, chemical, or physical agents on human health
- National Institute of General Medical Sciences (NIGMS): cancer-related basic biomedical research
- National Institute of Mental Health (NIMH): research on mood disorders in relation to cancer and cancer treatment
- National Institute of Neurological Disorders and Stroke (NINDS): research on brain, spinal cord, and pituitary cancers
- National Institute of Nursing Research (NINR): research across the cancer continuum

Burden of Illness and Related Health Statistics

Although significant progress has been made toward reducing the burden of cancer in America, cancer remains a leading cause of death, second only to heart disease—one of every four deaths is due to cancer.[1, 2] The economic cost of cancer in 2005 was estimated at more than $200 billion, including $74 billion in direct health care costs and more than $135 billion in indirect costs associated with lost productivity due to illness and premature death. The American Cancer Society estimated that, in 2009, there were about 1,479,350 new diagnoses of invasive cancer and 562,340 Americans died of cancer.[3] Moreover, the World Cancer Report indicates that cancer rates are set to increase at an alarming rate globally—specifically, they could further increase by 50 percent to 15 million new cases in the year 2020. Thus, cancer research is a major priority for NIH.[4]

There are signs of progress. U.S. death rates for the most common cancers and for all cancers combined have decreased significantly since 1995.[5] However, the annual number of cancer diagnoses is expected to almost double over the next 50 years, from 1.4 million to 2.6 million because of the growth and aging of the population. Increasing numbers of Americans are surviving cancer. NIH estimated that on January 1, 2005, 11.1 million living Americans had a history of invasive cancer.[6] Like cancer incidence, these numbers are likely to increase because of the anticipated growth and aging of the U.S. population.[7]

The most common cause of cancer-related death in the United States is lung cancer. The three most common cancers among men are prostate cancer, lung cancer, and colon cancer. For women, the three most frequently occurring cancers are breast, lung, and colon.[8]

Significant disparities in the U.S. burden of cancer have been documented through literature reviews, program reviews, and ongoing research. These disparities are discussed in *Minority Health and Health Disparities* later in this chapter.

NIH Funding for Cancer Research

Actual NIH funding support levels for cancer research were $5,570 million in FY 2008, and $5,629 million and $1,120 million in FY 2009, respectively, for non-ARRA (regular appropriations) and ARRA (Recovery Act appropriations). Click on the funding levels, which are live links, to produce detailed project listings. These lists are derived from the NIH Research, Condition, and Disease Categorization (RCDC) system. In addition, the table at the end of this chapter indicates some of the research areas involved in this investment (see *Estimates of Funding for Various Research, Condition, and Disease Categories*).

Summary of NIH Activities

Across NIH, cancer and cancer-related research activities are focused on two overarching goals: preempting cancer at every opportunity and ensuring the best outcomes for all. Specific objectives related to these goals include:

Preempting cancer at every opportunity:

- Understanding the causes and mechanisms of cancer
- Accelerating progress in cancer prevention
- Improving early detection and diagnosis
- Developing effective and efficient treatments

Ensuring the best outcomes for all:

- Understanding the factors that influence cancer outcomes
- Improving the quality of cancer care
- Improving quality of life for cancer patients, survivors, and their families
- Overcoming disparities in cancer prevention, diagnosis, treatment, and outcomes

NIH also is exploiting the potential of emerging technologies (e.g., molecular imaging, nanotechnology, and bioinformatics) in cancer research and care and is building the research infrastructure needed to expand knowledge and put new insights into practice.

Preempting Cancer at Every Opportunity

Understanding the Causes and Mechanisms of Cancer

Research that improves our understanding of the causes and mechanisms of cancer—from identifying novel risk factors to elucidating the processes of metastasis (the spread of cancer from the primary tumor site)—is essential for the development and application of interventions to preempt cancer's initiation and progression. NIH's plan for deciphering the causes and mechanisms of cancer includes fundamental research into cell signaling that can provide important insights into the molecular regulators of cell growth and differentiation in a range of tissues. In addition, NIH supports studies in molecular epidemiology to define complex risk factors, research on the tumor macroenvironment and microenvironment, understanding the role of altered gene expression in cancer progression, and exploring the roles of susceptibility genes in cancer risk and initiation.

A primary challenge for NIH is dissecting the molecular basis of cancer. The Cancer Genome Atlas (TCGA) is developing a comprehensive catalogue of the genetic changes that occur in cancers. The genomic information generated by TCGA could fuel rapid advances in cancer research and suggest new therapeutic targets. It also could suggest new ways to categorize tumors, which might allow clinical trials to focus on those patients who are most likely to respond to specific treatments. The TCGA network has selected more than 6,000 gene and microRNA (miRNA) targets for sequencing that represent both protein-coding genes and miRNAs.

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The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative identifies and validates therapeutic targets for childhood cancers beginning with acute lymphoblastic leukemia and neuroblastoma. Scientists

involved in this initiative recently identified mutations in a class of protein kinase genes called the janus kinases that predict relapse in high-risk children with acute lymphoblastic leukemia.[9]

Genetic susceptibility to cancer and cancer risk associated with environmental exposures also are important research topics. Using powerful new technologies to scan the entire human genome, NIH is conducting genome-wide association studies (GWAS) to identify unsuspected genetic variants associated with cancer risk (also see the section on *Genomics* in Chapter 3 for more information about GWAS). The Cancer Genetic Markers of Susceptibility (CGEMS) project, for example, is designed to identify genes that increase the risk of breast and prostate cancers. Similar efforts are directed at cancers of the pancreas, bladder, lung, and other organs. The results of these GWAS promise to provide novel strategies for cancer detection, prevention, and treatment.

Another major NIH initiative is the Sister Study, which is investigating environmental and genetic risk factors for breast cancer. This study involves a cohort of 50,000 sisters of women who have had breast cancer. These unaffected sisters are being followed over time, with periodic health updates. The women who develop breast cancer during the follow-up period will be compared with those who remained healthy to identify factors associated with increased cancer risk.

NIH also is supporting a network of Breast Cancer and the Environment Research Centers (BCERCs) to study the impact of prenatal to adult environmental exposures that may predispose a woman to breast cancer. One of the goals of the BCERCs is to develop public health messages to educate young girls and women who are at high risk of breast cancer about the role of specific environmental stressors in breast cancer and how to reduce exposures to those stressors. NIEHS is an NIH partner in support of this initiative as part of its Partnerships for Environmental Public Health initiative.

Other research into the causes and mechanisms of cancer has revealed that tumors function like organs, comprising many interdependent cell types that contribute to tumor development and progression. The relationship between tumors and their surrounding cellular environment evolves over time, strongly influencing tumor progression, metastatic potential, and responsiveness to treatment. The Tumor Microenvironment Network is a new NIH program focused on expanding our understanding of the role of the microenvironment in which a tumor originates and the critical role it plays during tumor development, progression, and metastasis.

Furthermore, interest is growing in the scientific community about the relationship between inflammation and cancer. Inflammation is a response to acute tissue damage, whether resulting from physical injury, infection, exposure to toxins, or other types of trauma. NIH actively is pursuing research on the linkages between carcinogenesis and alterations in the microenvironment induced by inflammation. Current research on inflammation suggests that pro-inflammatory conditions contribute to the development of several types of cancer, including lung, stomach, and liver cancers, and may lead to new treatment approaches (for example, research efforts focused on inflammatory and fibrotic diseases of the esophagus, stomach, colon, pancreas, and liver—all of which are risk factors for the development of cancer in these organs). The Cancer and Inflammation Program (CIP) constitutes a major component of NIH's inflammation and cancer initiative, which partners expertise in inflammation and immunology with cutting-edge cancer etiology and carcinogenesis research.

Systems biology and systems genetics also are promising new fields of study that will increase our understanding of the causes and mechanisms of cancer. These disciplines focus on biological and genetic networks that can be measured, modeled, and manipulated rather than focusing on the individual components. Because this research requires multidisciplinary teams of experts in biology, medicine, engineering, mathematics, and computer science, NIH launched the Integrative Cancer Biology Program (ICBP) to develop a framework for these activities. The ICBP has funded nine integrative biology centers around the United States to provide the nucleus for the design and validation of computational and mathematical models of cancer. Networks of genes can be found and their associations with cancer tested and quantified, and parallel association studies can be conducted in relevant human populations.

NIH is expanding its research portfolio related to the basic biology of tumor stem cells (also referred to as tumor-initiating cells). Tumor stem cells may be responsible for the recurrence of malignancy in some cancers. These cells often are

resistant to standard chemotherapeutic agents but may contain unique target molecules that may allow their eradication with novel molecular therapeutics. Progress has been made in identifying tumor stem cells in multiple myeloma, acute myelogenous leukemia, and breast cancer.

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Accelerating Progress in Cancer Prevention

Current research efforts into preventing cancer focus on modifying behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and interrupting the cancer process through early medical intervention. Dramatic developments in technology and a more complete understanding of the causes and mechanisms of cancer will enable us to provide more effective ways to prevent the disease. Identifying critical molecular pathways in precancerous lesions will provide new drug targets for preempting cancer. Transdisciplinary research will provide a more complete understanding of the interplay of molecular, behavioral, genetic, and other factors that contribute to cancer susceptibility. One example is the Partnerships for Environmental Public Health initiative, which is studying the health burden associated with risks in populations with inequities in environmental exposure and disease (including cancer); quantifying exposures to the many chemical, biological, and social stressors people experience over their lifetime at home, work, and play; and addressing health impacts of emerging environmental threats.

A major step forward in our efforts to prevent cancer has been the development of vaccines that target human papillomavirus (HPV). Persistent infection with HPV is recognized as the major cause of cervical cancer. Gardasil®, a U.S. Food and Drug Administration (FDA)-approved vaccine against HPV types 6, 11, 16, and 18—the viral types that cause approximately 70 percent of cervical cancers and 90 percent of genital warts—now is available. Other similar vaccines against HPV types 16 and 18 and/or additional subtypes are in development. These vaccines have the potential to save thousands of women's lives annually in the United States and several hundred thousand more each year worldwide. All of these vaccines resulted directly from epidemiological, basic, and preclinical research discoveries, as well as the development of a prototype HPV vaccine, by NIH scientists.

In an effort to reduce the cancer incidence, morbidity, and mortality associated with obesity, low physical activity, and poor diet, NIH has funded the Transdisciplinary Research on Energetics and Cancer (TREC) research centers, which foster collaboration among transdisciplinary teams of scientists. TREC centers are studying factors that lead to obesity and the mechanisms by which obesity increases the risk of cancer. The TREC initiative is connecting with a number of established initiatives in the areas of diet, physical activity, and weight and is integrated with the NIH Obesity Research Task Force Strategic Plan.

In an effort to reduce the cancer incidence, morbidity, and mortality associated with obesity, low physical activity, and poor diet, NIH has funded the Transdisciplinary Research on Energetics and Cancer (TREC) research centers, which foster collaboration among transdisciplinary teams of scientists.

Because most cases of lung cancer are caused by tobacco use and are, therefore, preventable, multiple NIH Institutes have co-funded seven Transdisciplinary Tobacco Use Research Centers (TTURCs), which seek to identify familial, early childhood, and lifetime psychosocial pathways associated with smoking initiation, use, cessation, and patterns of dependence. Research on the genetics of addiction, physiological biomarkers, and advanced imaging techniques should allow the development of individualized and community approaches to the prevention and treatment of tobacco-related diseases. The TTURC model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships.

We now know that the environment and behavioral lifestyles can play a critical role in the development of cancer. In fact, it was this discovery that led to a public health success story in the 20th century—the reduction in tobacco use and related diseases. By the mid-1950s, the mysterious and alarming epidemic in lung cancer, a disease that was almost nonexistent in 1900, was linked to smoking behavior. In the last decade, overall cancer death rates have 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. About 40 percent of this drop in overall cancer rates has been credited to the dramatic reduction in male smoking and male lung cancer deaths since 1991 (more than 146,000 fewer deaths during 1991 to 2003 alone). This success has been due to public-private partnerships and also is a trans-HHS victory, as significant research investments have been made over the last 50 years by NCI, NHLBI, NIDA, NIAAA, FIC, the Centers for Disease Control and Prevention (CDC), and the Agency for Healthcare Research and Quality (AHRQ). Without these investments, 40 million Americans might still be smoking today, hundreds of thousands of them would have died prematurely of a tobacco-related disease, and billions of dollars would have been spent on their treatment.[10]

The NIH-supported Community Clinical Oncology Program (CCOP) provides a network for greater participation in clinical trials on cancer prevention and treatment. There are 50 CCOPs and 13 Minority Based-CCOPs (CCOPs with 40 percent of their new patients from minority populations) currently funded in 35 states, the District of Columbia, and Puerto Rico. The program involves 3,645 physicians participating in 415 hospitals, working on more than 70 active prevention and control trials. The groups responsible for developing and implementing cancer prevention and control clinical trials are known as Research Bases; 14 Cooperative Groups and Cancer Centers have grants to serve as CCOP Research Bases.

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Improving Early Detection and Diagnosis

Detecting and diagnosing tumors early in the disease process, before the tumor becomes invasive and metastatic, can dramatically improve a patient's odds for successful treatment and survival, and prevent a large proportion of cancer deaths. Therefore, NIH seeks to accelerate the translation of basic research findings into sophisticated, minimally invasive procedures that harness imaging, genomic, proteomic, nanotechnology, and other advanced early-detection and diagnostic techniques.

Molecular profiling is an ongoing effort at NIH, from work at the bench to larger initiatives. In the area of molecular diagnostics, NIH has formed the Early Detection Research Network (EDRN) to bring a collaborative approach to the discovery, development, and validation of early-detection biomarkers for clinical application. Another NIH program, Strategic Partnering to Evaluate Cancer Signatures (SPECS), focuses on confirming, evaluating, and refining "signatures" derived from the molecular analysis of tumors (i.e., biomarkers detection) to improve patient management and outcomes. In addition, the Cancer Genome Anatomy Project (CGAP) focuses on determining the gene expression profiles of normal, precancerous, and cancerous cells to improve detection, diagnosis, and treatment. The CGAP website makes tools for genomic analysis available to researchers worldwide.

Yet another area of research that holds promise for advancing molecular diagnostics is proteomics—the study of complex arrays of proteins produced by cells and tissues. The completion of the Human Genome Project in 2003 has been a major catalyst for proteomics research, and NIH has taken a leading role in facilitating the translation of proteomics from laboratory research to clinical application through the Clinical Proteomic Technologies for Cancer (CPTC) initiative. The overall objective of this initiative is to build the foundation of technologies (assessment, optimization, and development), data, reagents and reference materials, computational analysis tools, and infrastructure needed to systematically advance our understanding of protein biology in cancer and accelerate basic science research and the development of clinical

applications. CPTC comprises three integrated programs: the Clinical Proteomic Technology Assessment for Cancer (CPTAC) network, the Advanced Platforms and Computational Sciences program, and the Proteomic Reagents and Resources Core.

Developing Effective and Efficient Treatments

Developing more effective, more efficient, and less toxic cancer treatments is at the heart of the NIH cancer research agenda. A strong understanding of the fundamental mechanisms leading to cancer development, progression, and metastasis will dramatically improve the identification of key biochemical pathways in the disease process as targets for treatment. Acceleration of target validation and the development of new treatment modalities will be possible through recent advances in biomedical science and technology. Rapid translation from development to delivery will ensure that promising treatments move safely and efficiently from preclinical investigation through late-stage clinical trials and into clinical practice. NIH is taking a multipronged approach to developing new therapies for cancer.

One innovative initiative, the NCI Experimental Therapeutics Program (NExT), combines the extensive expertise of cancer treatment and diagnosis in anticancer drug development with the dynamic NIH intramural research resources. This collaboration will rely on recent guidance from FDA concerning exploratory studies of investigational new drugs. Through NExT, extramural and intramural teams have prioritized a pipeline of targeted therapeutics for development. NExT promises to shorten the timeline for moving anticancer drugs from the laboratory to the clinic.

Another program, the Cancer Imaging Program (CIP), supports cancer-related basic, translational, and clinical research in imaging sciences. CIP initiatives include the development and delivery of image-dependent interventions for malignant and premalignant conditions; standardized models for the design of clinical trials that use imaging technologies; development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput screening; and development of imaging methods for cancer detection and treatment and for monitoring responses to therapy.

NIH launched the Comparative Oncology Program (COP) in an effort to improve the translational research process. Its mission was to provide an integrated mechanism by which naturally occurring cancers in pet dogs could be used to generate new information about cancer, translate biological concepts toward clinical application, and bring novel therapeutic options to the management of human cancers. As part of this effort, COP has established a multicenter collaborative network of extramural comparative oncology programs to design and implement preclinical trials involving pet animals to evaluate novel therapeutic strategies for cancer.

Ensuring the Best Outcomes for All

Research on the quality of cancer care is essential to ensuring the best outcomes for all who may be affected by cancer. Research in this area can include surveillance as well as epidemiological and cost-effectiveness studies. In addition, quality-of-life research increases our understanding of the impact of cancer on patients, survivors, and their family members—many of whom are themselves at increased risk for cancer due to shared cancer-causing genes, lifestyles, or environmental exposures. Dissemination research helps ensure that the knowledge gained through NIH-supported research is appropriately and effectively communicated to health care providers, policymakers, and the public. An additional goal related to overcoming health disparities in cancer incidence and outcomes is described in a later section of this chapter (also see the section on *Minority Health and Health Disparities* in Chapter 2).

NIH currently is engaged in making cancer a working model for quality-of-care research and the translation of research findings into practice. To this end, several collaborative projects have been initiated: (1) an interagency working committee, the Quality of Cancer Care Committee, which has fostered collaborative projects directly involving the Health Resources and Services Administration, AHRQ, Centers for Medicare and Medicaid Services, Department of Veterans Affairs, Indian Health Service, CDC, and other Federal health care research and delivery agencies; (2) the National Quality Forum, a major public-private partnership, to identify core measures of cancer care quality; (3) research on

outcomes measurement by the Cancer Outcomes Measurement Working Group and the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS); (4) studies on improving the quality of cancer communications; and (5) research to monitor patterns of treatment dissemination and quality of care through Patterns of Care/Quality of Care Studies. In addition, the NCI Community Cancer Centers Program (NCCCP) is researching how best to bring effective cancer treatments to patients in the communities where they live.

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The population of cancer patients surviving more than 5 years continues to grow. NIH continues to support research and education aimed at professionals who deal with cancer patients and survivors. The Office of Cancer Survivorship addresses the physical, psychosocial, and economic impacts of cancer diagnosis and its treatment and the need for interventions to promote positive outcomes in survivors and their families. Important early findings suggest long latencies for treatment-related effects, highlighting the need for extended follow up, early identification, and intervention before complications become more serious.

To improve the outcomes of cancer patients, advances in knowledge must be effectively disseminated to the public and health care providers. The Cancer Control P.L.A.N.E.T. portal is a collaborative effort aimed at providing access to data and resources that can help cancer control planners, health educators, program staff, and researchers to design, implement, and evaluate evidence-based cancer control programs. P.L.A.N.E.T. assists local programs with resources that help them determine cancer risk and burden within their State and helps States identify potential partners. P.L.A.N.E.T. also provides online resources for interpreting research findings and recommendations and accessing products and guidelines for planning and evaluation.

Infrastructure for Research

NIH places a high priority on technology development (also see the section on *Technology Development* in Chapter 3) to support both research and the application of research findings to improve health care delivery, emphasizing the areas of bioinformatics, cancer imaging, proteomics, and nanotechnology. As NIH-supported scientists begin to apply new discoveries to cancer prevention, early detection, and treatment, it increasingly will be important to integrate the tools and insights of research, science, and technology as effectively as possible.

The Cancer Biomedical Informatics Grid® (caBIG®) is an important initiative designed to accelerate research discoveries and improve patient outcomes by supporting the sharing of data and tools among researchers, physicians, and patients throughout the cancer community. caBIG® has developed and freely distributed more than 40 software tools with applications in basic and clinical research on cancer and other diseases. NIH is committed to extending caBIG® across the broader cancer research and care community. More than 1,500 individuals, representing more than 450 organizations in 13 countries, have so far participated in caBIG® projects. caBIG® technologies have been used to link the 65 Cancer Centers, the Community Cancer Centers Program, The Cancer Genome Atlas, other NIH Institutes, FDA, and international partners.

The Cancer Biomedical Informatics Grid® (caBIG®) is an important initiative designed to accelerate research discoveries and improve patient outcomes by supporting the sharing of data and tools among researchers, physicians, and patients throughout the cancer community.

The proposed Cancer Human Biobank (caHUB) is envisioned as a unique, centralized, nonprofit public resource to ensure an adequate supply of high-quality biospecimens and associated data acquired within an ethical framework. caHUB will promote standardization of biospecimen collection, distribution, data vocabulary, and informed consent, and will provide

an integrated information technology system to support all functions related to biospecimens. The Cancer Genome Atlas will serve as a pilot project for caHUB specimen collection and processing.

The new BIG Health Consortium™ will be a public-private partnership among key stakeholders in health care: patient advocates, health care providers, payers, product innovators, investors, and information technologists. Its mission is to show how and why personalized medicine works. Through a series of demonstration projects, BIG Health™ will model a new approach in which clinical care, clinical research, and scientific discovery are linked. The key enabler for this linkage is the informatics infrastructure that NIH has already developed—caBIG®.

The Alliance for Nanotechnology in Cancer, a comprehensive endeavor involving both public and private sectors, is designed to accelerate the application of the best capabilities of nanotechnology to cancer research. This initiative supports research on novel nanodevices to detect and pinpoint the location of cancer at its earliest stages, deliver anticancer drugs specifically to malignant cells, and determine in real time whether these drugs are effective in killing those cells. Programs of the Alliance include the Nanotechnology Characterization Laboratory; Cancer Nanotechnology Platform Partnerships; Centers of Cancer Nanotechnology Excellence; Innovative Technologies for Molecular Analysis of Cancer; and Tumor Stem Cells in Cancer Biology, Prevention, and Therapy.

NIH provides more than $300 million per year to 65 NCI-Designated Cancer Centers (CCs) around the country. Located in almost every State, CCs provide a foundation for cancer research and offer the latest evidence-based treatment. Support is given only to institutions that have demonstrated a critical combination of exceptional scientific leadership; collaborative, multidisciplinary research; and strong institutional commitment to promoting cancer research and improving cancer care. CCs and their affiliated academic institutions are the loci for more than 50 percent of the research grants, clinical trials, training projects, and other programs that receive NCI funding. Similarly, the majority of NCI's ARRA grants go to investigators affiliated with CCs; for example, more than 60 percent of CCs participated in an ARRA-funded program to provide Summer Research Experiences for Students and Science Educators.

Given the global burden of cancer and opportunities to identify new approaches in prevention and treatment through international collaborative research, NIH is strengthening health research infrastructure and building global research capacity through the International Tobacco and Health Research and Capacity Building Program. This program promotes transdisciplinary approaches to reduce the global burden of tobacco-related illness and is designed to promote international cooperation between U.S. investigators and scientists in low- and middle-income nations where tobacco consumption is a current or anticipated public health urgency. Because the overwhelming majority of smokers begin tobacco use before they reach adulthood, the program emphasizes research on determinants of youth smoking in diverse cultural and economic settings, as well as effective ways to prevent young people from starting to smoke.

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Personalized Medicine

Although understanding of the heterogeneous nature of cancer is expanding, cancer diagnosis remains relatively nonspecific and treatment continues to be largely based on histopathology and the tissue of origin. Early successes in developing therapeutics that target specific genetic defects (e.g., Herceptin®, Gleevec®, Erbitux) have provided impetus for a more comprehensive effort to define the biological effects of the myriad genomic and other information changes that drive cancer. Advances in many critical areas of cancer research are being synthesized into a vision of a future approach to health care called "personalized medicine," which will enable clinicians to use detailed molecular and clinical information about an individual's health (including biospecimens) to guide the selection of cancer therapies or preventive measures that are most likely to be safe and effective for that person.

The NIH vision of personalized medicine spans the entire cancer continuum, from prevention through survivorship. Investments in risk assessment, treatment, and infrastructure development already have yielded progress toward realizing that vision. Potential benefits of personalized medicine include increased understanding of individual risk factors; earlier detection and more accurate diagnosis of cancer; more effective, targeted treatment; increased likelihood of survival with improved quality of life; and implementation of high-quality, patient-centered cancer care through improved communication, informatics, and surveillance.

Accelerating progress toward a new era of personalized cancer medicine will require a mix of investigator-initiated research and large-scale, high-throughput projects performed by large teams of scientists and an array of new partnerships between cancer biologists and physical scientists to move new discoveries (including advances in biospecimens, bioinformatics, proteomics, epigenomics, and emerging technologies) from the bench to the bedside.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Initiatives and Major Programs

The Cancer Biomedical Informatics Grid® (caBIG®): The caBIG® initiative connects researchers and institutions to enable collaborative research and personalized, evidence-based care. More than 1,500 individuals representing more than 450 government, academic, advocacy, and commercial organizations have collaborated to develop a standards-based grid infrastructure (caGrid) and a diverse collection of interoperable software tools, enabling basic and clinical researchers to speed the translation of information from bench to bedside. Forty-nine of the 65 NCI-designated Cancer Centers and 8 of 10 organizations of the NCI Community Cancer Centers Program are actively deploying caBIG® tools and infrastructure in support of their research efforts. Additionally, caBIG® technology is adapted to power noncancer research initiatives such as the CardioVascular Research Grid. Ongoing collaborations with research and bioinformation organizations in the United Kingdom, China, and India are driving international adoption of caBIG® resources. The caBIG® infrastructure also supports a new health care ecosystem, BIG Health™, in collaboration with various stakeholders in biomedicine (e.g., government, academia, industry, nonprofits, and consumers) in a novel organizational framework to demonstrate the feasibility and benefits of personalized medicine. BIG Health™ will provide the foundation for a new approach in which clinical care, clinical research, and scientific discovery are linked.

→ For more information, see http://cabig.cancer.gov
→ For more information, see http://bighealthconsortium.org/
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Technology Development*
→ (E/I) (**NCI**)

Tobacco Control: NIH funds the Tobacco Product Assessment Consortium (TobPRAC) to develop methods and measures for product testing through a research and development contract. TobPRAC is advancing scientific knowledge about the toxic and addictive properties of tobacco products marketed by the tobacco industry with claims that imply reduced harm. In particular, this contract supports research to study the chemical and physical properties of different tobacco products, characterize the ways in which people's behavior affects their exposure to tobacco toxins, and develop methods and biomarkers to measure exposure and risk for tobacco-related diseases. The methods and findings developed under this contract will be made available to a wide range of stakeholders, including the scientific and public health communities, government, policymakers, and the general public. NIH and the American Legacy Foundation co-fund the Tobacco Research Network on Disparities (TReND). The mission of the network is to understand and address tobacco-related health disparities by advancing the science, translating that scientific knowledge into practice, and informing public policy. TReND is designed to stimulate new studies, challenge existing paradigms, and address significant gaps in research on understudied and underserved populations. It is the only national research network on tobacco and health disparities that offers a unique forum for stimulating scientific inquiry, promoting scientific collaborations, and evaluating the scientific evidence of research.

→ For more information, see http://cancercontrol.cancer.gov/tcrb/tob_prod_dev.html
→ For more information, see http://cancercontrol.cancer.gov/tcrb/trend/index.html
→ (E) (**NCI**)

Translational Research at the Aging/Cancer Interface: The NIH Translational Research at the Aging/Cancer Interface initiative was established in 2008 to enhance research in the overlapping areas of human aging and cancer by (1) integrating knowledge of basic processes in cancer biology and aging into clinical care of older patients with cancer ("bench to bedside"), and (2) exploring clinical observations from the patient care setting at more basic and molecular levels ("bedside to bench"). Research supported by this initiative holds potential for improving prevention, diagnosis, and disease management; improving the health and well-being of older adults at risk for or diagnosed with cancer; and decreasing the functional impairment and morbidity associated with cancer in this population.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-230.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-231.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIA**)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects

adipose tissue and alters hormonal control of sexual maturation. Endocrine distruptors, irradiation, and psychosocial elements also will be studied for effects.

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→ For more information, see http://www.bcerc.org/
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIEHS**, NCI) (GPRA)

The Sister Study: Environmental Risk Factors for Breast Cancer: The NIH Sister Study prospectively examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The frequency of relevant genes and shared risk factors is greater among sisters, increasing the ability of the study to detect risks. Researchers will collect data on potential risk factors and current health status, and will collect and bank blood, urine, and environmental samples for future use in studies of women who develop breast cancer or other diseases compared with those who do not. Analysis of new cases will assess the separate and combined effects of environmental exposures and genetic variations that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors like smoking, occupational exposures, alcohol, diet and obesity, and include analysis of phthalates, phytoestrogens, metals, insulin, growth factors, vitamins and nutrients, and genes in blood and urine. The study also allows investigators to examine a wide range of health outcomes of relevance to women, and to create a framework from which to test new hypotheses as they emerge. In addition to its focus on genetic and environmental causes of breast cancer, the prospective Sister Study tracks changes in health status over time. Among the chronic diseases currently studied are uterine fibroids and endometriosis, rheumatoid arthritis and other autoimmune diseases, thyroid disease, asthma, and cardiovascular diseases. As the cohort ages, the Sister Study will address aging-related health outcomes including osteoporosis, Parkinson's disease, and age-related cognitive decline.

→ For more information, see http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E/I) (**NIEHS**, NCMHD)

Surveillance, Epidemiology, and End Results (SEER): The SEER program provides essential data that support cancer research across NIH and collaborating agencies and organizations in the United States and around the world. SEER covers approximately 26 percent of the U.S. population, with information in its database on more than 5.7 million cancer cases. SEER registries routinely collect data on patient demographics, primary tumor site, morphology, extent of disease at diagnosis, and first course of treatment. All patients are followed annually for vital status and compilation of survival data. The SEER Program is the only comprehensive source of population-based data in the United States that includes stage of cancer at the time of diagnosis and survival rates by stage. It is the only population-based source of long-term incidence and survival data, having a 35-year history in most of its registries. SEER provides source data for the American Cancer Society Facts & Figures and the Annual Report to the Nation on the Status of Cancer. SEER is one of the most fundamental contributors to the cancer research infrastructure, adding more than 380,000 cases each year. The program sets national benchmarks for incidence and survival rates and is the primary source of reports on cancer death rates. The size of the database allows for analysis of rare cancers and cancer heterogeneity at both the tumor and patient level. The SEER database also includes prevalence information on the 11.4 million cancer survivors in the United States, allowing analysis by age and cancer site as well as time elapsed since diagnosis. There are more than 2,000 agreements executed annually for the public-use data and more than 3 million hits per month on the SEER Internet homepage.

→ For more information, see http://seer.cancer.gov
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E) (**NCI**)

Nanotechnology in Cancer: Nanotechnology innovation has been driven predominantly by physicists, engineers, and chemists; progress in cancer research comes primarily from discoveries of biologists and oncologists. The NIH Alliance for Nanotechnology in Cancer has set a goal of creating a community of cancer nanotechnologists who work together to develop nanotechnology approaches; apply them to the prevention, diagnosis, and treatment of cancer; and educate the medical community about opportunities enabled by cancer nanotechnology. The Alliance organized a session at 2009 American Association for Cancer Research meeting on Cancer Diagnostics Using Nanotechnology Platforms. Participants included high-profile investigators who work on the development of new nanodevices for in vitro diagnosis and in vivo imaging and clinicians who define oncology applications of those devices. Examples of this work include: PRINT, a technique allowing for controllable fabrication of nanoparticles; researching novel diagnostic techniques for proteins and DNA; developing implantable nanosensors; researching novel nanoparticle-based imaging agents and nanosensors; and developing nanotechnology-based cancer screening tools.

→ For more information, see http://nano.cancer.gov/
→ This example also appears in Chapter 3: *Clinical and Translational Research and Chapter 3: Technology Development*
→ (E/I) (**NCI**)

Molecular Profiling to Tailor Cancer Treatment: Molecular profiling is a powerful tool for identifying tumor subtypes and guiding clinical decisions to optimize patient benefit. NIH programs in this area include the Strategic Partnering to Evaluate Cancer Signatures (SPECS) Program, which is evaluating the clinical utility of molecular signatures and helping translate molecular data into improved patient management, and the Lymphoma/Leukemia Molecular Profiling Project. Several studies from these and other programs demonstrate the value of tailoring cancer treatment based on molecular characteristics of the patient and tumor. Gene expression profiling revealed distinct diffuse large B-cell lymphoma (DLBCL) subtypes, one of which exhibits activation of the pro-survival NF-κB pathway. A recent study confirmed that bortezomib, a drug that indirectly prevents NF-κB activation through proteasome inhibition, selectively enhances the effects of chemotherapy in this DLBCL subtype. A recent study revealed that head and neck squamous cell carcinomas (HNSCCs) associated with human papilloma virus (HPV)-16 are more responsive to treatment than HPV-negative HNSCCs. Results from a recent clinical trial indicate that advanced colorectal cancers should be tested for mutations in the KRAS gene. Patients with tumors housing KRAS mutations are unlikely to benefit from targeted therapies that block

epidermal growth factor receptor activity and should thus be spared the side effects and costs associated with these drugs. SPECS researchers recently developed an assay to classify breast cancer molecular subtypes and showed that when used in combination with clinicopathologic parameters (e.g., stage, grade), the assay improved prediction of prognosis and chemotherapy benefit.

→ Dunleavy K, et al. *Blood* 2009;113(24):6069-76. PMID: 19380866. PMCID: PMC2699229.
Fakhry C, et al. *J Natl Cancer Institute* 2008;100(4):261-9. PMID: 18270337.
Walther A, et al. *Nat Rev Cancer* 2009;9(7):489-99. PMID: 19536109.
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→ For more information, see http://www.cancerdiagnosis.nci.nih.gov/specs/index.htm
→ For more information, see http://llmpp.nih.gov
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NCI**)

NCI Imaging Programs: In addition to their applications in basic scientific discovery, imaging technologies contribute to cancer care through contributions to screening, diagnosis, disease staging, treatment guidance, treatment monitoring, and detection of cancer recurrence. NCI's imaging programs include the extramural Cancer Imaging Program (CIP), whose mission is to promote and support basic, translational, and clinical research in imaging sciences, and several intramural efforts within the Center for Cancer Research (CCR), such as the Molecular Imaging Program, Radiation Biology Branch, Radiation Oncology Branch, Center for Interventional Oncology, and NCI-Frederick Small Animal Imaging Program. The National Lung Screening Trial (NLST) is comparing two ways of detecting lung cancer: spiral computed tomography (CT) and standard chest X-ray. Both chest X-rays and spiral CT scans have been used to find lung cancer early. So far, neither chest X-rays nor spiral CT scans has been shown to reduce a person's chance of dying from lung cancer. This study will aim to show if either test is better at reducing deaths from this disease.

→ For more information, see http://imaging.cancer.gov
→ For more information, see http://home.ccr.cancer.gov/connections/features2.asp
→ For more information, see http://www.cc.nih.gov/centerio/index.html
→ For more information, see http://web.ncifcrf.gov/rtp/lasp/intra/saip/
→ For more information, see http://www.cancer.gov/NLST
→ This example also appears in Chapter 3: *Technology Development*
→ (E/I) (**NCI**) (GPRA)

Experimental Therapeutics for Cancer: The NCI Experimental Therapeutics Program (NExT) is an integrated drug discovery and development effort that concentrates research into a single robust pipeline that starts with discovery of promising compounds and leads, through a series of progressive steps, to first-in-human studies. The ultimate goal is to accelerate the translation of new oncology agents to the clinic.

→ For more information, see http://dctd.cancer.gov/About/major_initiatives_NExt.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NCI**)

Education and Outreach: NCI's Office of Communications and Education (OCE) provides comprehensive cancer information to those at risk and to patients, caregivers, and health care providers. This information ranges from prevention, through treatment, to end-of-life topics. For example, clinical sites across the country extensively use NIH print- and Web-based materials to support their educational programs. OCE also provides public affairs, publications, audiovisual exhibits, and Web development support to NCI Divisions, Offices, and Centers. The Cancer Information Service (CIS) effectively communicates information through a Partnership Program to help reach those with limited access to health information; an Information Service that provides cancer information by telephone, TTY, instant messaging, and e-mail; and a Research Program that helps advance health communication practices.

→ For more information, see http://www.cancer.gov/aboutnci/oce/
→ For more information, see http://cis.nci.nih.gov/
→ For more information, see http://cancer.gov/publications
→ For more information, see http://www.cancer.gov/cancertopics
→ For more information, see http://www.cancer.gov/espanol
→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (E) (**NCI**)

Clinical Trials Network: NCI-supported clinical trials networks share resources and pool data to promote and support the study of new cancer treatments, methods of cancer prevention and early detection, and quality-of-life and rehabilitation issues. The 65 NCI-designated Cancer Centers serve as a major platform for these trials. NCI is restructuring the Clinical Trials Enterprise. Initiatives include: Standard Terms of Agreement for Research Trials, the Clinical Trials Reporting Program, correlative studies (e.g., biomarkers, imaging, and quality-of-life studies) embedded in clinical trials, disease-specific and patient advocate steering committees, and acceleration of translational research. The Community Clinical Oncology Program recently stopped the Selenium and Vitamin E Cancer Prevention Trial. Initial data analysis showed that selenium and vitamin E supplements, taken either alone or together for an average of 5 years, did not prevent prostate cancer. Recent findings from NCI's Cooperative Group Program include a gene abnormality that predicts childhood leukemia relapse, the role of the ch14.18 monoclonal antibody in the treatment of high-risk neuroblastoma, and the usefulness of CT colonography in detection of large adenomas and cancers. Year 2 accomplishments of the NCI Community Cancer Centers Program include increased patient and physician involvement in NCI-sponsored trials, new methods for tracking minority accrual, and improved specimen collection. The Pediatric Oncology Branch of the NCI Center for Cancer Research (CCR) is coordinating a neurofibromatosis clinical trials program to develop effective therapies for this disease. The CCR also is conducting trials for patients with androgen-independent and metastatic prostate cancer using anti-angiogenic compounds as well as novel immunotherapies and immunologic strategies.

→ For more information, see http://restructuringtrials.cancer.gov/
→ For more information, see http://prevention.cancer.gov/programs-resources/groups/copt/programs/about
→ For more information, see http://www.cancer.gov/clinicaltrials/digestpage/SELECT/
→ For more information, see http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group
→ For more information, see http://target.cancer.gov/newsroom/news/01_07_09.aspx
→ For more information, see http://ncccp.cancer.gov
→ For more information, see http://content.nejm.org/cgi/content/full/359/12/1207
→ For more information, see http://ccr.cancer.gov
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NCI**) (GPRA)

Cancer Risk Assessment, Prevention, and Early Detection: The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial is a large-scale clinical trial to determine whether certain cancer screening tests reduce deaths from prostate, lung, colorectal, and ovarian cancer. Results of a recent PLCO study revealed that men offered annual prostate specific antigen (PSA) screening were more likely to be diagnosed with prostate cancer over a 10-year period, but no more likely to die from the disease than men in a control group. These results suggest that current screening tests may result in overdiagnosis and overtreatment of prostate cancer and highlight the need for biomarkers that can more accurately identify aggressive cancers that require intervention. The PLCO Etiology and Early Marker Studies (EEMS) allow investigators to access the nearly 3 million specimens gathered through PLCO. These include biologic materials and risk factor information collected from participants prior to diagnosis of disease, which are an invaluable resource for studying the origins and modes of action of cancer and identifying early markers of disease. The Early Detection Research Network (EDRN) is a consortium of more than 300 investigators representing divergent scientific disciplines, including genomics, informatics, and public health. EDRN was formed to facilitate the discovery, development, and validation of early detection markers and accelerate the translation of biomarker information into clinical applications. NIH also conducts a

strong research program in environmental and occupation exposures to uncover elements of gene-environment interactions that can lead to increased cancer risk.

→ Andriole GL, et al. *N Engl J Med* 2009;360(13):1310-9. PMID: 19297565.
→ For more information, see http://www.cancer.gov/newscenter/pressreleases/PLCOProstateResults
→ For more information, see http://www.parplco.org
→ For more information, see http://edrn.nci.nih.gov/
→ (E/I) (**NCI**)

Cancer Control P.L.A.N.E.T: The Cancer Control P.L.A.N.E.T. (Plan, Link, Act, Network with Evidence-based Tools) Web portal was launched collaboratively in 2003 by NIH, Agency for Healthcare Research and Quality, American Cancer Society, Centers for Disease Control and Prevention, Commission on Cancer, and Substance Abuse and Mental Health Services Administration. The portal now has been expanded, in collaboration with the Surveillance Action Group of the Canadian Partnership Against Cancer, to include Cancer Control P.L.A.N.E.T. Canada. The Canadian site follows the same design as the U.S. site, while engaging Canadian cancer control practitioners and researchers in usability testing to ensure that the Canadian site meets their needs. Both the Canadian and U.S. sites provide a single point of access to high-quality tools and resources from multiple national organizations that can be used to design, implement, and evaluate evidence-based cancer control plans and programs. They guide local programs to resources that help them determine cancer risk and cancer burden in their geographic areas. They also help identify potential partners and provide online resources for interpreting research findings and recommendations and accessing products and guidelines for planning and evaluation.

→ For more information, see http://cancercontrolplanet.cancer.gov
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E) (**NCI**)

Brain Tumor Research: NIH funds studies aimed at understanding the development and treatment of central nervous system and peripheral nervous system tumors, including medulloblastoma, neuroblastoma, and glioblastoma, as well as research on several inherited neurological tumor syndromes, including neurofibromatosis and tuberous sclerosis complex. In the past few years NIH has released a number of funding opportunity announcements (FOAs) related to brain tumor research. A FOA on understanding and preventing brain tumor dispersal has been particularly effective in stimulating this area of research and has led to exciting advances. NIH also funds clinical studies investigating therapy delivery to the brain and evaluating the safety and tolerability of various therapies, including immunological therapies, vaccine therapy, monoclonal antibodies, and combination therapies. The Surgical and Molecular Neuro-Oncology Unit within the NIH Division of Intramural Research investigates basic mechanisms of brain tumor development and chemotherapy resistance to find new therapeutic strategies, particularly for malignant gliomas. NINDS and NCI co-lead the Trans-NIH Brain Tumor Working Group.

→ For more information, see http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-08-048.html
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E, I) (**NINDS**, NCI)

Detection, Treatment, and Survivorship of Childhood Cancers: NIH has several ongoing programs to improve detection and treatment of childhood cancers, including the work of the NCI Pediatric Oncology Branch, the Childhood Cancer Survivors Study (CCSS), and the Pediatric Brain Tumor Consortium. Several of these programs are in collaboration with the Children's Oncology Group (COG). A recent COG study discovered that genetic alteration of the IKZF1 gene is associated with very poor outcomes in patients with B-cell progenitor acute lymphoblastic leukemia (ALL). These results should improve risk stratification for ALL patients, helping to ensure that those with high-risk disease

receive treatment of appropriate intensity and sparing low-risk patients unnecessary toxic effects. The Therapeutically Applicable Research to Generate Effect Targets (TARGET) initiative is cataloguing alterations in gene expression, gene sequences, and copy number of chromosome segments in pediatric cancers to discover cancer-specific changes. TARGET data are made available to the research community through a Web portal. TARGET researchers have discovered genomic alterations in pediatric ALL that are predictive of relapse and have identified activating mutations in a tyrosine kinase gene family for which small molecule inhibitors are available. Neuroblastoma TARGET specimens were used to confirm that approximately 10 percent of high-risk neuroblastoma cases have activating mutations in another tyrosine kinase, and a pediatric Phase I trial of an inhibitor of this kinase has been developed. The success of the TARGET approach in identifying novel therapeutic targets for ALL and neuroblastoma supports extension of this approach to other childhood cancers.

- → For more information, see http://www.cancer.gov/cancertopics/coping/childhood-cancer-survivor-study
- → For more information, see http://www.survivorshipguidelines.org
- → For more information, see http://home.ccr.cancer.gov/oncology/pediatric/
- → For more information, see http://www.pbtc.org/
- → For more information, see http://www.cancer.gov/NCICancerBulletin/NCI_Cancer_Bulletin_031808
- → For more information, see http://target.cancer.gov
- → This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- → (E/I) (**NCI**) (ARRA)

Animal Models Enhance Translational Research: The Comparative Oncology Program (COP) provides an integrated mechanism by which naturally occurring cancers in pets are used to generate new information about cancer, translate biological concepts into clinical applications, and support further development of human clinical trials. The NCI Center for Applied Preclinical Research (NCI-CAPR) and the Mouse Models of Human Cancer Consortium (MMHCC) aim to accelerate the development of therapeutics and diagnostics for human diseases by providing state-of-the-art animal models genetically programmed to mimic human disease development. Researchers associated with the MMHCC recently developed genetically engineered mouse models that mimic human osteosarcoma, endometrial cancer, and melanoma. Other mouse models have been used to study the response of T cells to tumor antigens and the contributions of chronic obstructive pulmonary disease to lung cancer among smokers. MMHCC also recently launched an integrated set of bioinformatics resources in conjunction with caBIG® to support research in preclinical models. A mouse model was used to elucidate cellular responses to Myc, a protein that plays an essential role in normal cell proliferation and also has oncogenic potential. A model of Myc-induced tumorigenesis revealed that tumor surveillance mechanisms are triggered by overexpression of the oncogene but not when the protein was deregulated without overexpression. This research provides insight into how tumor suppressor defense mechanisms can be circumvented, suggesting that keeping activated oncogenes at low levels may be important in the early stages of tumor development.

- → Murphy DJ, et al. *Cancer Cell* 2008;14(6):447-57. PMID: 19061836. PMCID: PMC2723751.
- → For more information, see http://ccr.nci.nih.gov/resources/cop/
- → For more information, see http://emice.nci.nih.gov
- → (E/I) (**NCI**)

Metabolism and Cancer: Disruptions in energy balance long have been implicated in the initiation and progression of cancer. Research on the population, organismal, cellular, and molecular levels is providing insight into the metabolic pathways that drive cancer. The Transdisciplinary Research on Energetics and Cancer (TREC) initiative supports multidisciplinary research on how obesity, poor diet, and low levels of physical activity increase cancer risk. The 96 developmental projects established to date have brought together investigators from numerous disciplines to study crosscutting problems related to energy balance and cancer. TREC's projects include molecular and animal studies of gastrointestinal, colon, and breast cancers; genetic epidemiology studies of the link between insulin resistance and colon polyps; animal and human studies of metabolic and behavioral responses to diet and exercise; and population studies to

determine etiology of, or behavioral risk factors for, obesity and to assess the association of obesity, exercise, weight reduction, or diet with biomarkers. TREC is poised for expansion into other research areas, including cancer survivorship, childhood obesity, genomics, and environmental aspects of obesity. A recent study suggests that mutation of genes that code for the metabolic enzyme isocitrate dehydrogenase, which helps convert biomolecules into a form of energy usable by the cell, may be an early event in the development of some malignant gliomas. Patients with these mutations had better outcomes than those with wild type isocitrate dehydrogenase genes, suggesting that mutational analysis of these genes may be useful as a clinical diagnostic tool. Intramural research efforts are breaking ground in the field of metabolomics, the systematic identification and quantitation of all metabolites in a given organism or biological sample.

→ Yan H, et al. *N Engl J Med* 2009;360(8):765-73. PMID: 19228619.
→ For more information, see http://cancercontrol.cancer.gov/trec/index.html
→ (E) (**NCI**)

Cancer Health Disparities Research Programs and Initiatives: NIH has expanded research on the basic biologic factors of cancer disparities to provide a foundation for minimizing risk, identifying targets, developing preventive and therapeutic interventions, and understanding how genetic susceptibility may be influenced by social, economic, race/ethnicity, and geographic factors. Thus, the research programs involve multidisciplinary teams, which contribute to understanding the etiology of cancer and build prevention and intervention evidence-based models to eliminate cancer disparities. Several programs at NIH address disparities along the cancer continuum from prevention to survival.

- The trans-disciplinary Geographic Management Program (GMaP) pilot initiative builds regional networks to support research, training, and infrastructure to develop state-of-the-art networks/centers to ensure a continuous supply of high-quality human biospecimens from multi-ethnic communities.
- The Community Networks Program engages communities experiencing cancer disparities to design, test, and evaluate evidence-based strategies to address critical needs, such as access to screening, mentoring, and training; policy development; and community outreach and education.
- The Patient Navigation Research Program builds partnerships to ensure that racial/ethnic minorities and underserved populations with abnormal cancer screening results receive appropriate care.
- The Community Clinical Oncology Program is a network for conducting cancer prevention and treatment clinical trials by connecting academic centers with community physicians.
- The NIH Centers for Population Health and Health Disparities catalyze transdisciplinary research to improve the understanding of complex interactions of biological, social, cultural, environmental, and behavioral factors that contribute to health inequities, and to develop and implement novel intervention strategies that are multilevel and multifactorial.
- The Tobacco Research Network on Disparities' mission is to understand and address tobacco-related disparities by advancing the science, translating that scientific knowledge into practice, and informing public policy.
- The Centers of Excellence in Cancer Communication Research continue to use best practices in communication science to extend the reach of biomedical benefits equitably throughout the population.

→ For more information, see http://crchd.cancer.gov/
→ For more information, see http://crchd.cancer.gov/cnp/background.html
→ For more information, see http://crchd.cancer.gov/pnp/pnrp-index.html
→ For more information, see http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCI**)

CISNET—A Resource for Comparative Effectiveness Research: The Cancer Intervention and Surveillance Modeling Network (CISNET) represents a quantum leap forward in the practice of modeling to inform clinical and policy decisions. While contemporary science has enabled the collection and analysis of health-related data from numerous sectors, enormous challenges remain to integrate various sources of information into optimal decision-making tools to inform public policy. Collaborative work on key questions promotes efficient collecting and sharing of the most important data and critical evaluation of the strengths and weaknesses of each resource. Providing results from a range of models, rather than a single estimate from one model, brings credibility to the process and reassures policymakers that the results are reproducible. CISNET is a consortium of NIH-sponsored investigators who use modeling to improve understanding of the impact of cancer control interventions (e.g., prevention, screening, and treatment) on incidence and mortality trends. The consortium's work informs clinical practice and recommended guidelines by synthesizing existing information to model gaps in available knowledge. CISNET provides a suite of models that are poised to determine the most efficient and cost-effective strategies for implementing technologies in the population. Four groups of grantees focus on breast, prostate, colorectal, and lung cancers using statistical simulation and other modeling approaches. Their models incorporate data from randomized controlled trials, meta-analyses, observational studies, epidemiological studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of these interventions.

→ For more information, see http://cisnet.cancer.gov/
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NCI**)

Collaborations Between Minority-Serving Institutions and Cancer Centers: The Minority Institution (MI)/Cancer Center (CC) Partnership (MI/CCP) is a flagship program that has been instrumental in establishing strong collaborations between minority-serving institutions (MSIs) and CCs. MI/CCP has fostered strong cancer research partnerships throughout the United States. This program established new cancer research curricula, recruited new faculty, increased awareness about health care disparities and cultural sensitivities, and developed programs and outreach efforts in educating underserved communities. The MI/CCP has provided research education and training to individuals at all levels including postdoctoral fellows, medical students, graduate students, students at master's level, and baccalaureate and high school students. Establishing new collaborations and partnerships in communities has been a hallmark of this program, culminating in increases in numbers of awarded grant applications and numbers of manuscripts, oral presentations, and poster presentations at both regional and national levels. Many research advances are emerging from the Partnership. For example, through the Morehouse School of Medicine and University of Alabama Partnership, researchers have identified a possible genetic cause for increased risk for a more advanced form of colorectal cancer in blacks that leads to shorter survival. Understanding the relationship between molecular defects and differences in colorectal cancer incidence, aggressiveness, and clinical outcomes is important in individualizing the treatment and in eliminating racial disparities.

→ For more information, see http://crchd.cancer.gov/research/miccp-overview.html
→ For more information, see http://clincancerres.aacrjournals.org/cgi/content/full/15/7/2406
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCI**)

Training for Cancer Research: The Center for Cancer Training is preparing a workforce to advance cancer research through a scientifically integrated approach. The Center coordinates intramural and extramural research training, career development, and educational opportunities. The Interagency Oncology Task Force Joint Fellowship Program, an NIH-FDA partnership, supports development of new medical products by training scientists in research-related regulatory review. The Cancer Education and Career Development (R25T) Program supports career development for early career investigators transdisciplinary sciences, producing a generation of researchers cross-trained in disparity research areas and poised to conduct team research. The Calabresi Award in Clinical Oncology (K12) Program brings together clinicians and

basic scientists to design and implement hypothesis-based therapeutic trials, promoting translation research findings from bench to beside. The Howard Temin Pathway to Independence Award in Cancer Research (K99/R00) assists early career basic scientists in transitioning from mentorship to independent research by providing funding to complete their fellowships, support their first investigator-initiated research programs, and launch their research careers. The Comparative Molecular Pathology Unit (CMPU) trains translational research investigators by incorporating interdisciplinary education in veterinary medicine with training in human biomedical research. Research Supplements to Promote Diversity in Health-Related Research create the foundation to attract and prepare qualified individuals from underrepresented and underserved populations and individuals with disabilities for careers in cancer research.

→ For more information, see http://www.cancer.gov/cct
→ For more information, see http://ccr.nci.nih.gov/resources/molecular_pathology/training.asp
→ This example also appears in Chapter 3: *Research Training and Career Development*
→ (E/I) (**NCI**)

Tumor Biology, Microenvironment, and Metastasis: The Tumor Biology and Metastasis Program supports research delineating the molecular mechanisms and signaling pathways involved in tumor progression, cell migration and invasion, angiogenesis (growth of blood vessels), lymphangiogenesis (formation of lymphatic vessels), and metastasis. Novel areas of research include the contributions of bone marrow-derived cells to tumor formation, progression, and metastasis; the role of dormant cells and their microenvironment; the role of host tissue microenvironment in organ-specific metastasis; characterization of the heterogeneity within the tumor microenvironment; and the characterization of cancer as a systemic disease. The Tumor Microenvironment Network (TMEN) investigates mechanisms of tumor-stroma interactions in human cancer. (Stroma is the connective tissue that supports or surrounds other tissues and organs.) In addition to delineating the role of host stroma in carcinogenesis, TMEN investigators are generating novel reagents that can be shared with the research community. The Cancer Immunology/Hematology Program supports research on the cellular and molecular characterization of tumor stem cells, which are minor populations of tumor cells that may be responsible for recapitulating all the cell types in a given tumor and causing metastasis due to their unique self-renewal properties. In FY 2008, NIH sponsored two RFAs on tumor stem cells aimed at enhancing synergistic research between basic scientists and translational scientists working on tumor stem cells. In addition, a program announcement for Stem Cells and Cancer was released to stimulate efforts to isolate and characterize tumor stem cells from a large spectrum of tumors to understand better the progression of malignant disease.

→ For more information, see http://tmen.nci.nih.gov
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-019.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-020.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-165.html
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NCI**)

Testing for Reproductive Tumors in the National Toxicology Program's Carcinogenesis Bioassay: Perinatal Dosing: The National Toxicology Program (NTP) evaluates substances for a variety of health-related effects. Two-year studies in laboratory rodents remain the primary method by which chemicals or physical agents are identified as having the potential to be hazardous to humans. In 2006, NTP convened a workshop on Hormonally Induced Reproductive Tumors, Relevance of Rodent Bioassays to discuss the adequacy of rodent models used in the 2-year bioassay for detecting reproductive tumors. The workshop recommended that in utero and lactational exposures could be added to the chronic bioassay depending upon what is known about the mode of action. For detecting tumor types such as testicular germ cell tumors, this recommendation was especially strong. In utero and lactational exposures should be considered for mammary tumor studies if there are any developmental effects associated with a substance under study that involved endocrine tissues, steroid receptor binding, a change in mammary gland morphology, or altered timing of vaginal opening. NTP has conducted such perinatal exposures on cancer bioassays in the past, but only when there was special justification

for such a design to be adopted. A new default design in which dosing will start in pregnancy and be continued throughout life or to the end of a 2-year period now has been adopted unless there is a good scientific reason not to undertake such a study. NTP has initiated studies to obtain data for constructing physiologically based pharmacokinetic (PBPK) models in rodents and nonhuman primates. It is planning studies to explore the long-term consequences of perinatal exposure to Bisphenol A to understand the potential impact to humans of the developmental changes reported in numerous laboratory animal studies. It is hoped that the PBPK models will link information from rodent studies with primate studies, and potentially with human outcomes.

→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (O) (**NIEHS**)

Systems Biology and Systems Genetics: The Integrative Cancer Biology Program (ICBP) provides new insights into the development and progression of cancer as a complex biological system. Teams of researchers at ICBP Centers are integrating the disciplines of biology, medicine, engineering, math, and computer science (e.g., computational biology). ICBP Centers use a spectrum of innovative technologies such as genomics, proteomics, and molecular imaging to generate and validate computational and mathematical models. These in silico models describe and simulate the complex process of cancer, from the basic cellular processes through tumor growth and metastasis, and allow researchers to run "virtual" experiments, which ultimately should lead to better cancer prevention, diagnostics, and therapeutics. The centers have produced more than 35 computational models, developed a validated siRNA library of cancer genes, and created a set of nationally distributed breast cancer cell lines that reflect the heterogeneity of human breast cancer. Equally important to our understanding of cancer is systems genetic research (systems biology + genetics). Networks of genes can be found and their associations tested and quantified with parallel association studies on relevant human populations.

→ For more information, see http://icbp.nci.nih.gov/
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NCI**)

Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer Care: The purpose of the Cancer Research Network (CRN) is to enhance research on cancer epidemiology, prevention, early detection, and control in the context of health care delivery systems. CRN combines established research groups affiliated with 14 health care delivery organizations that provide comprehensive care to a racially and ethnically diverse population of nearly 11 million individuals. CRN has developed strong research capabilities in several areas: developing and applying innovative methods to collect and interpret data from both conventional and electronic medical records systems; assembling large samples of patients with documentation of patient characteristics and longitudinal data on receipt of health services and clinical and quality-of-life outcomes; collecting and integrating complex data from patients, providers, and organizations to examine issues in health care delivery from multiple perspectives; quantifying the effect of key factors in the delivery process that may determine quality and outcomes of care; and conducting studies on behavioral and systems-based interventions to improve the delivery of care in community-based health care delivery systems. The Breast Cancer Surveillance Consortium (BCSC) is a research resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. The BCSC is a collaborative network of seven mammography registries with linkages to tumor and/or pathology registries. The Consortium's database contains information on 7,521,000 mammographic examinations, 2,017,869 women, and 86,700 cancer cases.

→ For more information, see http://crn.cancer.gov
→ For more information, see http://breastscreening.cancer.gov/
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Clinical and Translational Research* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**NCI**)

HIV/AIDS-Related Malignancies: The Activities to Promote Research Collaborations in AIDS-Associated Malignancies initiative provides administrative supplements for multidisciplinary collaborations among NCI grantees and AIDS investigators. Recently issued program announcements solicit applications to advance understanding of the risks, development, progression, diagnosis, and treatment of malignancies observed in individuals with underlying HIV infection or AIDS. One of these focuses on the role of HIV/AIDS in the etiology, prevention, and treatment of hepatocellular carcinoma. The Fogarty International Clinical Research Scholars Program pairs U.S. students with students from low- and middle-income countries (LMICs) to conduct research on AIDS-related malignancies in LMICs. The goal is to build research capacity in both countries and build intellectual bridges between the United States and LMICs. HIV/AIDS and cancer registries in three states were linked to study cancer risk among HIV-infected persons (initially AIDS-free) over time. Kaposi sarcoma and non-Hodgkin lymphoma incidence have declined markedly in recent years, likely reflecting treatment-related improvements in immunity, while incidence of some non-AIDS-defining cancers have increased. A study of nearly 500,000 individuals diagnosed with AIDS revealed that the risk of human papillomavirus (HPV)-associated cancers is increased among persons with AIDS and that this risk rises with increasing immunosuppression. Persons with AIDS also were found to be at increased risk for melanoma, Merkel cell carcinoma, and sebaceous carcinoma. The U.S. HIV/AIDS Cancer Match Study found that risk of sqamous cell carcinoma of conjunctiva and other eye cancers is increased among adults with AIDS.

→ Engels EA, et al. *Int J Cancer* 2008;123(1):187-94. PMID: 18435450.
Guech-Ongey M, et al. *Int J Cancer* 2008;122(11):2590-3. PMID: 18224690.
Lanoy E, et al. *AIDS* 2009;23(3):385-93. PMID: 19114864. PMCID: PMC2728602.
Chaturvedi AK, et al. *J Natl Cancer Inst* 2009;101(16):1120-30. PMID: 19648510. PMCID: PMC2728745.
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-454.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-243.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-244.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-245.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-455.html
→ For more information, see http://www.cancer.gov/cancertopics/types/AIDS
→ For more information, see http://oham.cancer.gov
→ (E) (**NCI**, FIC)

Genome-Wide Association Studies: With unprecedented speed, researchers have used an approach called genome-wide association studies (GWAS) to explore genetic variants and their complex relationships to human health and disease. GWAS research has linked a stunning number of genetic variants to common conditions—more than 130 in 2008 alone. For example, the obesity epidemic and its related health conditions pose a great challenge for the Nation. In 2008, the Genetic Investigation of Anthropometric Traits consortium identified six genes associated with body mass index, a key indicator for obesity. Also in 2008, three GWAS of lung cancer implicated several genes already known to be linked to nicotine addiction. In a feat that would not have been possible without the power of whole genome analysis, the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium in 2009 gathered data from participants in long-running studies to reveal genetic variants associated with an increased risk of stroke. Identification of genetic variants associated with common diseases opens new windows into the biology of health and disease. This work also raises the possibility of someday using genetic testing, in combination with family history, to identify at-risk, pre-symptomatic individuals who might benefit from personalized screening and preventive therapies.

→ For more information, see http://www.genome.gov/27528559
→ For more information, see http://www.genome.gov/27529231
→ For more information, see http://www.genome.gov/27531390
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E, I) (**NHGRI**, **NIDDK**, **NCI**, **NIA**, **NHLBI**, **NIMH**, NINDS)

Exemplary Current Studies and Projects

Genome-Wide Association Studies of Cancer Risk: The Cancer Genetic Markers of Susceptibility (CGEMS) project is a signature initiative that uses genome-wide association studies (GWAS) to identify genetic variants and mechanisms associated with cancer risk. Understanding these variants and mechanisms may lead to new preventive, diagnostic, and therapeutic interventions. CGEMS investigators have pinpointed genetic variants associated with elevated prostate cancer risk as well as variants associated with increased breast cancer risk. The same genetic variant was shown to be involved in increased prostate, colon, and other cancers, suggesting a common mechanistic pathway for susceptibility to a variety of cancers. Another GWAS project, the Cohort Consortium, is a unique extramural/intramural collaboration that allows Consortium partners to share access to data on 37 cohorts comprised of 4 million people from diverse populations. Each cohort contains extensive information on known or suspected risk factors and biospecimens collected pre- and post-diagnosis. The large number of study subjects permits the detection of modest genetic effects, as well as studies of variants involved in less common cancers. One cohort within the Consortium, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort, includes about 2.9 million specimens. These pre-diagnostic specimens provide a valuable resource for studies of cancer etiology and early detection. Researchers can correlate changes in molecular profiles associated with the onset of different types of disease, thereby providing valuable insights into the actual mechanisms of human carcinogenesis.

- → For more information, see http://cgems.cancer.gov
- → For more information, see http://epi.grants.cancer.gov/Consortia/cohort.html
- → For more information, see http://www.parplco.org
- → This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*
- → (E/I) (**NCI**)

Development of Image-Guided Interventions: Image-guided interventions (IGI) provide therapy that can minimize trauma and improve patient outcomes. They are applicable in procedures such as biopsy, surgery, radiation treatment, vascular interventions, and guidance during delivery of devices, drugs, cells, or genes. These improved capabilities particularly are important in light of the shifting trend in medicine toward a model of early, presymptomatic detection of disease. Representative of ongoing research is an effort to improve image-guided surgical removal of tissue using optical coherence tomography (OCT). Recent studies suggest that OCT optical imaging techniques may have a significant impact on breast cancer biopsy and treatment. High-resolution OCT image guidance could help ensure complete surgical removal of tumors and adequate diagnostic biopsy sampling. As other biomedical imaging modalities, such as MRI, improve the ability to detect small suspicious lesions, OCT can be used to guide a biopsy needle precisely to tumor tissue and cells and enable sampling of these smaller nonpalpable lesions. In preliminary studies, surgically removed lumpectomy specimens from more than 65 patients have been imaged with OCT in the operating room. When compared to post-operative histopathology, OCT yielded a sensitivity of 100 percent and a specificity of 82 percent and demonstrates the potential of OCT as a real-time method for the intraoperative margin assessment in breast-conserving surgeries.

- → Nguyen FT, et al. Meeting Abstract: Optical coherence tomography (OCT) as a diagnostic tool for the real-time intraoperative assessment of breast cancer surgical margins. *Cancer Res* 2009;69: 802.
- → This example also appears in Chapter 3: *Technology Development*
- → (E) (**NIBIB**) (GPRA)

Cancer Epidemiology Biomarkers and Prevention: The long-term Sister Study looks at the environmental and genetic characteristics of women whose sisters have had breast cancer to identify factors associated with developing breast cancer. A pilot study that was part of the Sister Study shows that women who maintain a healthy weight and who have lower perceived stress may be less likely to have chromosome changes associated with aging than obese and stressed women. Recently, NIH funded a study looking at 94 women whose breast cancer had spread or returned. Researchers asked the women whether they had ever experienced stressful or traumatic life events. The categories ranged from traumatic stress

to some stress to no significant stress. The comparison revealed a significantly longer disease-free interval among women reporting no traumatic or stressful life events.

→ For more information, see http://www.niehs.nih.gov/news/releases/2009/sister-study.cfm
→ For more information, see http://www.nlm.nih.gov/medlineplus/magazine/issues/winter08/articles/winter08pg6b.html
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E/I) (**NCI**, NIA)

Microchip Captures Early Circulating Cancer Cells: Malignant cancers shed cells that enter the circulation, travel to other areas of the body, and often grow into secondary tumors, or metastases. Indeed, metastases are responsible for the great majority of cancer deaths. It is estimated that 70,000 men per year are diagnosed with recurrent prostate cancer after prostatectomy, as shown by rising prostate surface antigens. For these men, the ability to detect and characterize the malignant cells in the blood may enable personalized therapy. Researchers are developing a technology to facilitate quantitative detection of circulating tumor cells (CTCs). They have engineered a microchip with a large surface area of an adhesion molecule that binds CTCs from whole blood, making detection of CTCs more reliable than previous approaches. They are analyzing molecular and genomic information in the CTCs to identify new biomarkers to customize treatments that are personalized for the patients and to predict treatment outcomes. The NIH-supported research has the potential to eliminate or greatly reduce cancer deaths due to metastases.

→ Nagrath S, et al. *Nature* 2007;450(7173):1235-9. PMID: 18097410.
→ For more information, see http://www.nibib.nih.gov/HealthEdu/eAdvances/31July08
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIBIB**)

Molecular Theranostics: New Technologies for the Diagnosis and Treatment of Diseases: The concept of combining a therapeutic with a diagnostic agent rapidly is evolving and goes beyond traditional diagnostic tests that screen or confirm the presence of a disease. With specialized molecular imaging techniques and biomarkers, theranostics might predict risks of disease, diagnose disease, and monitor therapeutic response leading to real-time, cost-effective treatment. NIH supports a number of teams that are developing novel theranostics and approaches that can be applied in clinical studies of human patients. A team of chemists and neurosurgeons at the University of Michigan is developing highly specific, dye-loaded nanoparticles capable of delivering targeted photosensitizers to improve the survival of brain tumor patients. This technique will allow neurosurgeons to visualize the brain tumors for surgical resection of the main tumor mass while eradicating remaining tumor cells through a process known as photodynamic therapy. These particles also contain imaging contrasting agents to visualize response to therapy.

→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIBIB**)

Cell Senescence and Aging: Cell senescence is a mechanism prominent in aging processes and widely considered as an anti-cancer preventive or treatment therapy. Studies focus on such topics as senescence induced by the Ras gene and its potential to halt or slow tumor progression, the role of the retinoblastoma protein pRb in cellular senescence and the development of a wide range of cell types and associated tumors, telomere attrition, the role of oxidative stress, epigenetic regulation, and DNA damage and repair. NIA-supported studies on Werner syndrome (a condition characterized by accelerated aging in children) and the role of the WRN protein in telomere metabolism are improving our understanding of basic cellular mechanisms that act to suppress development of specific aging characteristics and cancer.

→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
→ (E/I) (**NIA**)

New Biomaterials System Programs Cells in situ to Fight Cancer: In the body's immune response to foreign invaders, dendritic cells signal and activate other cells to initiate a generalized inflammatory response. Cell-based cancer vaccinations build on this natural tendency by isolating and activating a patient's dendritic cells using tumor antigens, and then injecting the reprogrammed cells back into the patient. The activated dendritic cells travel home to the lymph nodes and promote an antitumor response. Unfortunately, most transplanted dendritic cells die. Additionally, reprogrammed cells partially lose their effectiveness after injection back into the body. Thus, multiple rounds of injections are required to achieve significant effect. To address these limitations, investigators developed a multifunctional in situ dendritic cell reprogramming system composed of polymeric biomaterials that release cytokines to attract dendritic cells already within the lymph nodes into the biomaterials. The dendritic cells are then activated by the biomaterials. The biomaterials reduce their cytokine release at a controlled rate so that after activation, the dendritic cells will migrate away from the biomaterials back home to the lymph nodes and present tumor antigens to T cells found there. In a mouse model this sophisticated system provided protection from tumor development equal or superior to that provided by traditional cancer vaccines without the complications and costs of ex vivo cell manipulation and transplantation. The new system also provided much better control over the number of dendritic cells than traditionally generated cancer vaccines. This study demonstrates a powerful new application for polymeric biomaterials that could be used in the future against cancers and other diseases.

→ Ali OA, et al. *Nature Materials* 2009;8(2):151-8. PMID: 19136947. PMCID: PMC2684978.
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIDCR**)

New Model Reveals Novel Molecular Strategies in the Fight to Overcome Oral Cancer: Oral and pharyngeal carcinomas are the ninth most common cancer worldwide, with more than 35,000 new patients and more than 7,500 deaths each year in the United States alone. The 5-year survival rate has improved only marginally over the past 40 years. There is an urgent need for new options for these patients. Emerging information on the deregulation of normal molecular mechanisms that result in the cancer's progression provides the possibility of new mechanisms-based therapeutic approaches for these aggressive oral malignancies. NIH scientists recently used a two-step chemical carcinogenesis model and found that the drug rapamycin exerted a remarkable anticancer activity. It decreased the tumor burden of mice having early and advanced tumors, and even brought about the regression of recurrent squamous cell skin cancers. The scientists reported that the persistent activation of mTOR, the mammalian Target of Rapamycin, occurs frequently in head and neck cancer patients and that its inhibition by rapamycin causes regression of human oral cancer tumors implanted in mice. Because chemically induced animal cancer models often better reflect the complexity of the clinical setting, the scientists developed an oral-specific chemical carcinogenesis mouse model. In this model, activation of mTOR is an early event in precancerous lesions; rapamycin treatment can halt the malignant conversion of precancerous lesions and promote the regression of advanced carcinogen-induced oral squamous cell carcinomas (SSCs). Significance: The development of this SCC carcinogenesis model demonstrates that the use of mTOR inhibitors may provide a novel molecular-targeted strategy for chemoprevention and treatment of oral squamous cell cancer.

→ Amornphimoltham A, et al. *Clin Cancer Res* 2008;14(24):8094-101. PMID: 19073969.
Czerninski R, et al. *Cancer Prevention Res* 2009;2(1):27-36. PMID: 19139015.
→ For more information, see http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/OralCancer/
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (I) (**NIDCR**)

New Targets Identified for Intervention in the Development of Head and Neck Cancers: Over the last decade, cancer researchers have made significant progress in defining the molecular pathways involved in the development of head and neck squamous cell cancer. Studies that identify and characterize “key players” hold tremendous promise for the future

treatment of these devastating cancers and ultimately improve the overall survival and quality-of-life for afflicted patients. One such key player is a family of proteins known as Wnt. Aberrant activation of the Wnt pathway has been found to be associated with cancer development and progression. Wnt promotes initiation of cancer by increasing the nuclear accumulation of ß-catenin, an integral component of Wnt signaling, to activate target genes downstream. However, the mechanism of ß-catenin recruitment to the Wnt target gene promoter largely is unknown. In an elegant study, the researchers discovered that ß-catenin interacted with two other molecules (commonly called TBL1 and TBLR1), leading to the recruitment of ß-catenin to the promoter of Wnt target genes. Decreasing TBL1 or TBLR1 via genetic knock-down did not affect the nuclear accumulation of ß-catenin, but it did inhibit ß-catenin significantly from binding to Wnt target gene promoter and the expression of Wnt target genes associated with tumor development. Moreover, depletion of TBL1 or TBLR1 inhibited invasive growth of tumor cells. These results provide fundamental knowledge about tumor genesis by revealing two new components required for nuclear ß -catenin function. Targeting these molecules can have important therapeutic implications for head and neck cancer.

→ Li J, Wang C-Y. *Nat Cell Biol* 2008;10(2):160-9. PMID: 18193033.
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NIDCR**)

Inflammation, Immunology, and Cancer Virology: Several NIH programs are working to facilitate and rapidly translate advances in the discovery, development, and delivery of immunologic and antiviral approaches to improve the prevention and treatment of cancer, cancer-related viral diseases, and AIDS-associated malignancies. One notable example with implications for therapeutic cancer vaccine development is the discovery that co-delivery of Interleukin (IL)-15 with vaccines results in a more robust immune response both at the time of vaccine administration and in the event that the target antigen is encountered a second time. (IL-15 is a protein that regulates activation and proliferationn of some cells in the immune system.) IL-15 currently is in production for large-scale clinical trials. The human papillomavirus (HPV) Vaccine Trial in Costa Rica is a multiyear effort designed to test the ability of virus-like particle vaccines, originally developed at NIH, to protect against HPV16/18 infection. In addition to evaluating vaccine efficacy, the trial is examining broader measures of vaccine impact as well as immunity, natural history of HPV, and cervical neoplasia.

→ Oh S, et al. *Proc Natl Acad Sci U S A* 2008;105(13):5201-6. PMID: 18362335. PMCID: PMC2278231.
→ For more information, see http://ccr.nci.nih.gov
→ For more information, see http://home.ccr.cacner.gov/coe/immunology/
→ For more information, see https://ccrod.cancer.gov/confluence/display/CEHCV/Home
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E/I) (**NCI**, NIAID, OAR, ORWH)

Massage Therapy May Ease Pain and Improve Mood in Advanced Cancer Patients: People with advanced cancer often experience pain that causes physical and emotional distress, which leads to a decrease in functional ability and quality of life. Symptom relief is an important part of end-of-life care, and small studies have suggested that massage therapy may benefit people with advanced cancer. In a study funded in part by NIH, researchers investigated the benefits of massage vs. simple touch therapy (placing both hands on specific body sites) in patients with advanced cancer. This multisite study—conducted at 15 U.S. hospices in the Population-Based Palliative Care Research Network—included 380 participants with advanced cancer who were experiencing moderate to severe pain. Participants were randomly assigned to receive 6 30-minute treatment sessions of either massage or simple touch therapy over a 2-week period. The study found that both the massage and simple touch groups experienced statistically significant improvements in pain relief, physical and emotional distress, and quality of life. Immediate improvement in pain and mood was greater with massage than with simple touch; however, sustained effects of these therapies were not observed. The study's findings indicate that massage therapy may provide some immediate relief for patients with advanced cancer. The findings also suggest that simple touch, which can be provided by family members and volunteers, may benefit these patients.

→ Kutner JS, et al. *Ann Intern Med* 2008;149(6):369-79. PMID: 18794556. PMCID: PMC2631433.
→ For more information, see http://nccam.nih.gov/research/results/spotlight/110608.htm
→ (E) (**NCCAM**)

Other Notable Examples

2009 Institute of Medicine Report, The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors: The recently released IOM report, *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors,* reviews U.S. interest and investment in global health. This report is particularly timely and useful given the major changes in global health that have occurred since the last IOM report, *America's Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests*, was released in 1997. These changes include unprecedented interest and large fiscal commitments to global health by the U.S. government and nongovernmental sectors. The IOM leveraged the contributions of 18 NIH ICs to undertake this update with additional financial support from several key private and public entities. The study makes the case for why U.S. agencies and private sector entities should invest more heavily in global health. The report has five key recommendations that can inform NIH investments in global health in the coming years:

- Scale up existing interventions to achieve significant health gains
- Generate and share knowledge to address health problems endemic to the global poor
- Invest in people, institutions, and capacity-building with global partners
- Increase U.S. financial commitments to global health
- Set the example of engaging in respectful partnerships

The IOM panel was chaired by Dr. Harold Varmus and Ambassador Thomas Pickering. A preliminary report, titled *The U.S. Commitment to Global Health: Recommendations for the New Administration*, was released in December 2008. In May 2009, the final report, titled *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*, was released.

→ For more information, see http://www.iom.edu/Reports/2009/The-US-Commitment-to-Global-Health-Recommendations-for-the-Public-and-Private-Sectors.aspx
→ For more information, see http://www.iom.edu/Reports/2008/The-US-Commitment-to-Global-Health-Recommendations-for-the-New-Administration.aspx
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (O) (**FIC**, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS)

Research Tools for Genomic Studies of Cancer: The Cancer Genome Atlas (TCGA) is developing a publicly accessible, comprehensive catalog of the many genetic changes that occur in cancers. Tumor and matched normal samples are analyzed for genetic changes such as chromosome rearrangements and gene mutations; gene expression changes, including changes in expression patterns of microRNAs, as well as epigentic modifications (differences in the chemical modifications of DNA that influence gene expression). All data, including pre-publication data, are freely available through the TCGA website and are compatible with the cancer Bioinformatics Grid (caBIG®). The first TCGA project, which focused on brain cancer (glioblastoma multiforme), demonstrated the feasibility and impact of large-scale NIH-coordinated cancer genome analysis. Comprehensive characterization of ovarian cancer with other tumor types will follow. The goal of the Cancer Genome Anatomy Project (CGAP) is to provide cancer researchers with tools, resources, and information derived from studies that are characterizing differences between cancer and normal cells. The CGAP website provides access to data, bioinformatic tools, and information about available full-length cDNAs and short hairpin RNA clones. These resources are helping scientists conduct the research necessary to improve detection, diagnosis, and

treatment of cancer. In the past year, new projects that explore molecular characterization through novel technologies were added as part of the Cancer Genomic Technology Initiative (CGTI). REMBRANDT is the national portal for molecular, genetic, and clinical data associated with several thousand primary brain tumors. This framework provides researchers the ability to answer basic questions related to a patient or patient populations and view integrated datasets in a variety of contexts.

→ For more information, see http://cancergenome.nih.gov/index.asp
→ For more information, see http://cgap.nci.nih.gov/
→ For more information, see https://caintegrator.nci.nih.gov/rembrandt/
→ For more information, see http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm
→ This example also appears in Chapter 3: *Genomics*
→ (E/I) (**NCI, NHGRI**, NINDS) (ARRA)

NIH Strategic Plans Pertaining to Cancer

National Cancer Institute (NCI)

- *NCI Strategic Plan for Leading the Nation*
- *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2008*
- *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2009*
- *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2010*
- *Advancing Basic, Translational and Clinical Research: A Strategic Plan for the Center for Cancer Research*

National Institute of Dental and Craniofacial Research (NIDCR)

- *NIDCR Strategic Plan*
- *NIDCR Implementation Plan*

National Center for Complementary and Alternative Medicine (NCCAM)

- *Expanding Horizons of Health Care: Strategic Plan 2005-2009*

John E. Fogarty International Center (FIC)

- *Pathways to Global Health Research: Strategic Plan 2008-2012*

Office of AIDS Research (OAR)

- *FY 2008 Trans-NIH Plan for HIV-Related Research*
- *FY 2009 Trans-NIH Plan for HIV-Related Research*
- *FY 2010 Trans-NIH Plan for HIV-Related Research*

Other Trans-NIH Plans

- *Report of the Brain Tumor Progress Review Group*
  (NCI, NINDS)

[1] For more information, see www.cancer.org.
[2] For more information, see www.cdc.gov/nccdphp/burdenbook2004/index.htm.
[3] American Cancer Society; 2009.
[4] National Cancer Institute. 2006 Fact Book. Bethesda, Md.: U.S. Department of Health and Human Services, 2007. For more information, see http://obf.cancer.gov/financial/attachments/06Factbk.pdf.
[5] NCI; 2006.
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[7] Edwards BK, et al. *Cancer* 2002;94:2766-92. PMID: 12173348.
[8] NCI; 2006.
[9] Mullighan CG, et al. Proc *Natl Acad Sci U S A* 2009;106:9414-8. PMID: 19470474. PMCID: PMC2695045.
[10] Thun MJ, Jemal A. *Tob Control* 2006;15:345-7. PMID: 16998161.

Neuroscience and Disorders of the Nervous System

Often viewed as the last biological frontier, the brain is perhaps the most intriguing organ in the human body. For centuries, efforts to understand the human brain ultimately have yielded to its inaccessibility, protected by the skull and invisible to X-rays; and to its complexity, with some 100 billion interconnected neurons. Yet, over just the last few decades, major advances in noninvasive brain imaging technologies have allowed researchers and clinicians to peer inside the living, working human brain. Such sophisticated neuroimaging techniques have become invaluable research tools, revealing structural and functional changes in nervous system disorders that point to their causes and that could aid in their diagnosis and treatment. In 2009, the NIH Blueprint for Neuroscience Research launched a bold new initiative to apply these cutting-edge technologies to a long-held grand challenge in neuroscience: mapping the connectivity of the entire living human brain. The Human Connectome Project will combine the use of multiple brain imaging methods with demographic and genetic data, as well as information on sensory, motor, cognitive, emotional, and social function, in hundreds of healthy adults. Neuroimaging already has improved clinical outcomes in important ways by, for example, identifying stroke patients likely to benefit from the clot-busting drug tPA and guiding neurosurgery and device implantation. Brain imaging also has been used experimentally in conjunction with neurofeedback training, in which patients learn to control pain perception, and a similar approach might one day help substance abusers control drug cravings. The Human Connectome Project will build on and accelerate such advances, and may yield unprecedented insights into fundamental questions in neuroscience that rest on understanding the connections between brain areas and how they are altered in disorders such as autism, schizophrenia, and epilepsy.

Introduction

Composed of the brain, spinal cord, and nerves of the body, the nervous system underlies perception, movement, emotions, learning and memory, and other functions essential to individual and societal well-being. The nervous system interacts with all other organ systems and is affected by countless diseases, conditions, and environmental factors. Moreover, with limited capacity for self-repair, the nervous system is particularly vulnerable to damage due to injury or infection, and its repair mechanisms are poorly understood. Neuroscience research seeks to understand the nervous system and its functions in health and disease. Given its intrinsic complexity and central role in physiology and behavior, this understanding must necessarily come from multiple perspectives. Accordingly, neuroscience research spans many disciplines, from genetics to physiology to psychology, and applies tools from areas such as molecular biology, anatomy, computer sciences, and imaging technologies.

Neuroscience is a unifying theme in NIH research. The intramural and extramural programs of several ICs have a major focus on the nervous system, but the full scope of neuroscience activities extends to components of research portfolios across most of NIH, reflecting the multidisciplinary nature of the field and the importance of the nervous system to many aspects of human health, development, and disease. These activities often involve collaborative efforts combining the unique strengths and expertise of individual ICs, and to reinforce such collaborations, NIH established the Blueprint for Neuroscience Research.[11] The Blueprint accelerates neuroscience research through training programs, the development of shared tools and resources, and initiatives to address challenges in neuroscience that transcend the mission of any single IC.

The principal aim of NIH research in neuroscience is to reduce the burden of diseases that affect the nervous system, including a broad range of neurological disorders; disorders affecting cognitive, emotional, and behavioral function; diseases and conditions that impair the primary senses; and developmental and age-related disorders. Whether led by single investigators or conducted through centers and consortia, NIH neuroscience research includes basic science studies of normal function and development in both humans and animal models, translational research that develops medications or other therapies, and clinical trials that test interventions in patients.

Nervous system disorders include common killers and major causes of disability like stroke, multiple sclerosis, and epilepsy, as well as hundreds of less common diseases, such as lysosomal storage disorders, spinal muscular atrophy, muscular dystrophies, inherited neuropathies, neurofibromatosis, tuberous sclerosis, and Rett and Tourette syndromes. Many neurological disorders have genetic or developmental origins. Others result from trauma to the nerves, spinal cord, or brain; from autoimmune, infectious, or systemic disease; from tumor growth in nervous system tissues (also see the section on *Cancer* in Chapter 2); or from neurodegenerative processes as in Parkinson's disease, frontotemporal dementia, and amyotrophic lateral sclerosis (ALS). NIH research on neurological diseases, largely supported by NINDS, seeks to uncover their causes and mechanisms and to develop drugs and other treatments or preventive strategies. This research also aims to understand the multiple aspects of the nervous system that disease can affect and has shared support across NIH for basic science studies of the cerebral vasculature, electrochemical signaling in neurons and other cells, mechanisms of development and cell death, neuromuscular function and motor control, and behavior and cognition. In addition, NIH works to enhance the lives of those disabled by stroke, traumatic brain injury, spinal cord injury, and other neurological conditions through research supported by NICHD's National Center for Medical Rehabilitation Research and other ICs on neuroplasticity, recovery and repair of motor and cognitive function, and rehabilitative and assistive strategies and devices (also see the section on *Life Stages, Human Development, and Rehabilitation* in Chapter 2).

Brain disorders affecting cognitive, emotional, and behavioral function include schizophrenia and psychoses; autism spectrum disorder and other developmental disorders; mood and anxiety disorders; addiction to nicotine, alcohol, and other substances; and post-traumatic stress disorder, eating disorders, attention deficit hyperactivity disorder, and other behavioral disorders. These disorders have complex causes involving genetic and environmental influences and their interactions throughout life. Through research efforts led by NIAAA, NIDA, NIMH, and other ICs, NIH focuses on uncovering these causes, understanding their neural and behavioral bases, and developing therapies and interventions for treatment and prevention. NIH research also seeks to understand the acute and long-term effects of abused substances on the nervous system.

Sight, smell, balance, and our other primary senses, as well as the ability to communicate, allow interactions with a changing external environment. NEI and NIDCD sponsor most of NIH's research on basic mechanisms of sensory perception and communication and on diseases and conditions affecting the eyes and vision, hearing and balance, voice, speech and language, taste and smell, and somatosensory function, including the senses of temperature and touch. Although vital to survival, the sensation of pain also is symptomatic of many diseases with origins in and outside the nervous system, from migraine and other headaches to cancer-related pain conditions. NIH pain research is led by NIDCR and the NIH Pain Consortium, which coordinates research across NIH on pain and its treatment (also see the section on *Chronic Diseases and Organ Systems* in Chapter 2). NIH-supported research also studies the many ways the nervous system interacts with and regulates changes in the body's internal environment. This research, including efforts supported by NHLBI and NIDDK, focuses on areas such as circadian rhythms and sleep disorders; neuroendocrine processes that regulate stress responses, hormone levels, and motivational states; and the neural basis of appetite and feeding, which is of key relevance to slowing the increasing rates of obesity worldwide.

Nervous system disorders may arise in development, strike young adults, or emerge late in life. NICHD and other ICs sponsor research on the development of the nervous system and its functions. This research encompasses studies of structural birth defects, including spina bifida and other neural tube defects and associated conditions such as hydrocephalus. NIH also invests in research on developmental disorders like cerebral palsy, Down syndrome, autism spectrum disorder, and other causes of intellectual and learning disabilities. Nervous system development continues into early adulthood in humans, and developmental processes and their external influences contribute to mental fitness and disease risk later in life, including the risk for addiction, which often begins in childhood or adolescence. At the other end of the lifespan, with key support from NIA, NIH research on the aging nervous system includes studies of age-related disorders such as Alzheimer's disease and other dementias, as well as environmental and lifestyle factors affecting neurological, cognitive, and emotional health in aging populations.

Across all ages, the nervous system is a common target of exposure to toxins, pollutants, and other agents, whose effects range from acute reactions to developmental disorders and neurodegeneration. NIH-sponsored research on the consequences of such environmental exposures for nervous system function and disease includes a particular focus by NIEHS. NIH also considers diseases of the nervous system from a global point of view. Coordinated primarily by FIC, NIH supports neuroscience-related research around the world in unique populations and environments and on factors contributing to disparities in disease vulnerability and treatment quality and access, such as socioeconomic conditions and infectious disease.

Burden of Illness and Related Health Statistics

Nervous system disorders take an enormous toll on human health and the economy. Even rare disorders carry a substantial collective burden, as they often have an early onset and long duration, and the stigma commonly attached to neurological and mental illnesses further compounds individual and societal impact. According to 2005 estimates, neurological disorders strike more than 1 billion people worldwide, account for 12 percent of total deaths, and result in more disability than HIV/AIDS, ischemic heart disease, or malignant tumors.[12] In the United States, stroke is the third leading killer of adults and results in annual medical and disability costs totaling nearly $70 billion.[13] Each year, another 1.4 million Americans sustain traumatic brain injury (TBI), the leading cause of death and long-term disability in young adults,[14] with direct and indirect costs reaching approximately $60 billion in 2000.[15] Head injury also accounts for an estimated 20 percent of combat-related injuries in modern wars, and blasts are a leading cause of TBI in military personnel.[16]

In a given year, approximately 12.5 million American adults (or 1 in every 17) suffer a debilitating mental illness.[17,18] Mental disorders result in more disability for U.S. adults than any other class of medical illness,[19] and a conservative estimate places the total direct and indirect annual costs of mental illness at more than $300 billion.[20] In 2008, among persons in the United States ages 12 years or older, 18.3 million were classified with dependence on or abuse of alcohol, and 7.0 million were classified with dependence on or abuse of illicit drugs.[21] The overall social and economic burden of substance abuse continues to rise, with annual costs related to alcohol and illicit drug abuse totaling $235 billion[22] and $181 billion,[23] respectively.

Mental illness and neurological disorders affect people of all ages. An estimated 17 percent of U.S. children have a developmental or behavioral disorder such as autism spectrum disorder, intellectual disability, or attention deficit hyperactivity disorder.[24] Current demographic trends project a growing burden from age-related diseases of the nervous system as populations benefit from increased longevity. One in 7 U.S. adults ages 72 years and older has dementia, and estimates of the prevalence of Alzheimer's disease range from 2.4 million to 5.1 million, a number expected to rise to as many as 13.2 million by 2050 unless effective interventions are developed.[25,26]

NIH Funding for Neuroscience and Disorders of the Nervous System

Actual NIH funding support levels for research in neuroscience and disorders of the nervous system were $5,224 million in FY 2008, and $5,320 million and $848 million in FY 2009, respectively, for non-ARRA (regular appropriations) and ARRA (Recovery Act appropriations). Click on the funding levels, which are live links, to produce detailed project listings. These lists are derived from the NIH Research, Condition, and Disease Categorization (RCDC) system. In addition, the table at the end of this chapter indicates some of the research areas involved in this investment (see *Estimates of Funding for Various Research, Condition, and Disease Categories*).

Summary of NIH Activities

Neurodevelopment, neuroplasticity, and neurodegeneration are common themes that reflect shared biological processes found in many aspects of nervous system function and disease. In this section, these themes will serve to highlight selected examples of activities and progress in neuroscience research enabled by NIH, as well as challenges and future opportunities. Additional activities and initiatives exemplify how collaborative approaches are facilitating advances in basic, translational, and clinical neuroscience. More information, as well as more examples, can be found in the bulleted list at the end of this section.

Neurodevelopment: Periods of Growth, Maturation, and Vulnerability

Complex interactions between gene expression and function, endocrine and other physiological processes, neuronal activity, and external influences guide the development of the nervous system. From the early differentiation of its many neuronal and other cell types to the establishment of billions of synapses, or connections between neurons, each step in nervous system development is vulnerable to disruption by disease, injury, or environmental exposures. NIH research across all stages of neurodevelopment is leading to a better understanding of neurological, mental, and behavioral function in health and disease throughout life, as well as to new treatments and preventive strategies.

During early human embryonic development, a flat surface of cells destined to become the brain and spinal cord rolls into a structure called the neural tube. Defects resulting from improper neural tube formation, including spina bifida and anencephaly, are among the most common birth defects. Sufficient dietary folic acid before conception and during early pregnancy can reduce the risk of neural tube defects, but although the United States and other countries now fortify their food supplies with folic acid, not all neural tube defects are prevented, indicating that other risk factors also may contribute. NIH-supported research recently conducted in collaboration with investigators in Ireland showed an elevated risk for neural tube defects in children born to mothers with low blood levels of vitamin B12 shortly before and after conception. This research suggests that, in addition to folic acid, women expecting to conceive may be able to further reduce the risk of neural tube defects by consuming sufficient amounts of vitamin B12.

Recent NIH-supported research also provided strong evidence for an inexpensive and easily prescribed treatment to prevent cerebral palsy in children born prematurely. Cerebral palsy refers to a group of nonprogressive neurological disorders that result from damage to the developing fetal or infant brain, leading to abnormal control of movement and posture. Early preterm birth is a major risk factor for cerebral palsy and is associated with approximately one-third of all cases. NIH supported the largest, most comprehensive effort to date to determine whether magnesium sulfate, a drug routinely given to prevent seizures in women with preeclampsia and to delay preterm labor, could protect against the risk for cerebral palsy when given to pregnant women likely to give birth prematurely. The randomized, controlled clinical trial showed that severe or moderate cerebral palsy occurred significantly less frequently after treatment with magnesium sulfate as compared to placebo.

Both genetic and environmental factors influence nervous system development and function, and a growing area of neuroscience research focuses on how genes and the environment interact in a range of disorders including multiple sclerosis, Parkinson’s disease, depression and other mood and anxiety disorders, addiction, and autism spectrum disorders. As part of the NIH Collaborative Study on the Genetics of Alcoholism (COGA), a longitudinal study during adolescence—a stage of life marked by increased susceptibility to alcohol use disorders—has identified several genes associated with the risk for alcoholism and related behaviors such as anxiety, depression, and other types of drug dependence. Other NIH-supported studies focus on how environmental influences, such as parenting quality, exposure to abused drugs, socioeconomic status, and neighborhood characteristics, affect brain development and behavior, contributing to the goal of understanding the role of these factors in drug abuse initiation.

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NIH supports broad efforts to understand how autism spectrum disorders (ASD) may arise from combined effects of genetic vulnerabilities and exposure to potentially harmful environmental agents during key periods of development. As one example, the Early Autism Risk Longitudinal Investigation (EARLI) is following a cohort of 1,200 mothers who have children diagnosed with ASD through a subsequent pregnancy (also see the section on Autism Centers of Excellence in Chapter 4). This study will help determine the contribution of environmental factors, such as in utero exposure to organic pollutants, to ASD risk in families that already may be genetically susceptible to the disorder. Although all forms of ASD are characterized by challenges in three core domains of functioning (social impairments; communication difficulties; and restricted, repetitive, or stereotyped patterns of behavior), considerable heterogeneity exists across individuals with ASD in these and other clinical features, suggesting the contribution of multiple developmental trajectories and causal factors. One cross-cutting theme highlighted in the Interagency Autism Coordinating Committee (IACC) Strategic Plan for ASD Research is the need to understand this heterogeneity, which could lead to new insights into the causes of ASD, improved diagnosis, and more targeted intervention strategies. To address this need, NIH issued a series of funding opportunity announcements titled, "Research to Address the Heterogeneity in Autism Spectrum Disorders," for research on ASD measurement, biomarkers and biological signatures, immune and central nervous systems interactions, genetics and genomics, environmental risk factors, and intervention and treatment. Funds from the American Reinvestment and Recovery Act of 2009 will support this collaborative effort among several NIH ICs, the largest single funding opportunity for ASD research in NIH history. NIH intends to use additional ARRA funds to jumpstart many of the short-term objectives of the IACC Strategic Plan, through the Challenge Grants in Health and Science Research Program (RFA-OD-09-003), and Grand Opportunity grants (RFA-OD-09-004).

The human brain continues to mature into early adulthood, and understanding normal nervous system development is essential to knowing when, where, and how developmental processes can go wrong. In the NIH Magnetic Resonance Imaging (MRI) Study of Normal Brain Development, NIH-supported researchers at 7 collaborating institutions collected brain scans and clinical and behavioral data from more than 500 healthy infants, children, and adolescents over the course of 7 years, providing important baseline information that could identify signs of atypical brain development. The data gathered and analytical tools developed for this longitudinal study are available to the broader research community in a Web-based, searchable database. An improved understanding of the normal course of human brain development also is yielding insights into behavioral and cognitive development and function across the lifespan. For example, previous brain imaging studies have shown that one of the last brain areas to fully mature is the prefrontal cortex, an area important for decision-making and impulse control. This aspect of brain development may contribute to impulsive behavior in teenagers and help explain their increased susceptibility to drug abuse and addiction. NIH-supported research also recently has shown a delay of about 3 years in the development of the prefrontal cortex in children with attention-deficit/hyperactivity disorder (ADHD) as compared to age-matched children without the disorder.

NIH investigators already are using knowledge about human brain and behavioral development to guide research on interventions to treat nervous system disorders or to reduce their risk of occurrence later in life. For example, researchers reporting delayed development of the prefrontal cortex in ADHD now are studying the effects of ADHD treatment on the rate of cortical maturation. To reduce the incidence of substance abuse disorders in children and adolescents, NIH supports evidence-based research to target an array of risk factors and behaviors through developmentally appropriate preventive strategies, including interactive Web-based programs and encouraging physical activity as a way to counter drug use. The NIH Underage Drinking Initiative similarly supports research on underage drinking and its risk factors, as well as efforts to develop and implement effective interventions, all within a developmental framework.

Neuroplasticity: Substrates for Change and Repair

Throughout development, and even once its basic structure and circuitry have been established, the nervous system retains a remarkable capacity to adapt to changes in the body's internal environment and external conditions and events. This capacity, known as plasticity, alters the function and activity of neuronal networks, and it occurs at many levels of the nervous system, from altered signaling at synapses thought to underlie learning and memory, to large-scale functional and neuroanatomical reorganization accompanying the loss of a limb or sensory organ. Plasticity enables beneficial adaptations, including acquiring new knowledge, improving performance, and adjusting behavior. However, it also can lead to maladaptive changes, and neuroplasticity-related mechanisms contribute to a range of disorders, including mood disorders, addiction, chronic pain, and obesity. By better understanding these mechanisms, researchers may be able to both harness their therapeutic potential and limit their deleterious consequences.

Mood disorders, such as depression and anxiety, are associated with changes in the function of brain networks involved in emotion, and treatments targeting plasticity mechanisms could alleviate these disorders and reduce their recurrence. NIH researchers previously demonstrated that low doses of ketamine—an anesthetic that blocks brain receptors known to be involved in neuroplasticity—can act as a rapid antidepressant, lifting symptoms within hours, while conventional medications take weeks. Further research now has identified changes in brain activity in depressed patients that correlated with their responsiveness to ketamine's rapid antidepressant effects, and that therefore may reflect brain network changes underlying their depression. NIH also supports research on treatments for mood disorders through clinical trial networks. Ongoing studies include the Lithium Use for Bipolar Disorder (LiTMUS) trial and the Combining Medications to Enhance Depression Outcomes (CO-MED) trial, which will examine for the first time whether two different medications, when given in combination as the first treatment step, will enhance remission and provide better sustained benefits than treatment with a single medication. Other NIH support for research on mood disorders includes a new program for Innovative Approaches to Personalizing the Treatment of Depression.

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Neuroplasticity underlies a range of changes in brain function and behavior involved in the development and persistence of addiction. In particular, the same brain mechanisms mediating reward-related learning also contribute directly to addiction. NIH-supported investigators recently mapped the genomic effects of chronic cocaine use in the reward center of the mouse brain using a powerful new technique known as ChIP-chip, which can identify epigenetic changes, or lasting changes in gene expression caused by mechanisms other than alterations in the underlying DNA sequence. Such analyses of the genetic and epigenetic effects of cocaine and other abused substances may point to new targets for intervention. Stress-related systems in the brain also contribute to addiction and relapse. NIH researchers have investigated specific brain chemicals that mediate behavioral stress responses for their contributions to alcohol dependence, and they are building on their insights to develop new treatments. In one study, alcohol-dependent patients who recently had stopped drinking were treated with a drug that blocks signaling through the receptor for a stress-related molecule called neurokinin 1. The treatment reduced alcohol cravings, improved overall well-being, and reduced blood levels of stress hormones. It also altered brain activity in ways that suggested a potential for reducing the likelihood of relapse in alcohol-dependent individuals. As a promising alternative for treating addiction, NIH also supports the development of vaccines for drug addiction, an approach called immunotherapy. Unlike conventional small molecule therapy, which acts on neural signaling pathways involved in drug addiction, in immunotherapy, a vaccine targets the drug itself. The vaccine stimulates the production of drug-specific antibodies, which bind the drug in the blood and prevent its entry into the brain. This diminishes or completely blocks the drug's reinforcing effects on addiction-related neural signaling, and therefore may lead to reduced drug use. In a recent Phase II clinical trial, a vaccine developed against nicotine showed strong positive results in promoting abstinence among study participants who achieved sufficient antibody levels. Other innovative treatment approaches under development with NIH support include medications to promote new learning and diminish

conditioned responses to drug-related cues, which may help counter cravings or alter expectations of reward associated with drug use.

In a recent Phase II clinical trial, a vaccine developed against nicotine showed strong positive results.

Plasticity also is an important factor in the development and persistence of pain disorders. Opioid analgesics are the most powerful medications currently available to treat chronic pain, but they can unfortunately result in addiction, tolerance, and physical dependence, limiting their value in some patients. One focus of NIH-supported research to develop new treatments is the cannabinoid signaling system. Just as the brain produces natural opioid-like compounds, it also produces natural compounds that act on the same receptors as the neuroactive component in the cannabis plant (marijuana). Cannabinoid signaling modulates neuronal activity and plasticity and also plays a role in modulating pain. Research suggests that selective activation of cannabinoid signaling pathways may provide analgesia with minimal psychotropic effects. NIH-supported researchers also have reported new findings on the mechanisms that lead to neuropathic pain induced by nerve injury. Most available treatments for neuropathic pain target neurons. In contrast, the new findings highlight the role of certain enzymes released by non-neuronal cells called glia, which are involved in immune and inflammatory responses to nerve injury. Future treatments targeting glia may provide a way to halt the maladaptive signaling cascade that results in neuropathic pain. NIH also supports efforts to exploit adaptive plasticity at the level of brain networks for therapeutic pain intervention. Using real-time brain imaging, researchers have shown that patients with chronic pain can learn to exert voluntary control over activation of a particular brain region involved in pain perception and its regulation, effectively reducing the impact of their painful sensations.

Although plasticity can lead to changes in neural activity patterns throughout life, the adult human brain and spinal cord have a limited capacity to actually replace or repair neurons that are lost or damaged by injury or disease. An exciting area of neuroscience research focuses on ways to overcome these limitations to promote recovery and restore function. For example, spinal cord injury often leads to permanent paralysis and loss of sensation below the site of injury because damaged nerve fibers are unable to regrow across the injury site. NIH supports research to understand the mechanisms that restrict such regrowth and to design strategies that integrate new nerve fibers into spinal circuitry. In one study, researchers showed in a mouse model of spinal cord injury that self-assembling nanofibers reduced scar formation and cell death, promoted regeneration of nerve fibers across the injury site, and improved functional recovery. As another example, researchers long thought the adult human brain could not generate new neurons. However, more current research has shown that the production of neural stem cells—which can become new neurons or other types of brain cells—continues into adulthood in certain brain regions. NIH supports research on the role of these cells in normal function, injury, and disease, as well as on the potential for treatments that tap into this intrinsic renewal mechanism. The results of a recent study suggest that stem cells isolated from the adult brain may be able to replace lost sound-detecting cells in the inner ear, providing a foundation for future treatments of hearing loss.

Neurodegeneration: Fighting the Effects of Age, Exposure, and Disease

The progressive loss of neurons is a common endpoint of many diseases and insults to the nervous system. Such degeneration presents challenges to developing strategies to slow and prevent cell death, protect remaining neurons, and possibly replenish those that are lost. Recent and ongoing NIH research on neurodegenerative diseases focuses on understanding their biological and environmental causes and on efforts to develop interventions that not only alleviate their symptoms, but that may slow or even stop disease progression.

Alzheimer's disease is the most common cause of dementia in the elderly, though some inherited forms of the disease become symptomatic in middle age. Scientists now believe that damage to the brain begins well before symptoms appear. NIH-supported basic research on Alzheimer's disease mechanisms has contributed in recent years to industry development of new drug treatments. NIH also supports translational research efforts to move basic research findings toward clinical

applications. A recent study reported that a grape seed-derived extract reduced Alzheimer's disease-like neuropathology and cognitive decline in a mouse model, indicating promise for further therapeutic development of this extract, which is likely to be safe and well-tolerated in people. In addition, NIH supports clinical trials for treating and slowing Alzheimer's disease, many of which are coordinated through the Alzheimer's Disease Cooperative Study (ADCS), involving nearly 70 sites in the United States and Canada. In 2009, five new clinical trials were underway through the ADCS. One study will examine the clinical utility of intravenous immunoglobulin, which contains naturally occurring antibodies targeting beta amyloid, a protein implicated in Alzheimer's disease. Other studies include a multicenter trial to evaluate home-based assessment methods for Alzheimer's disease prevention research, and trials to test treatment with the omega-3 fatty acid DHA, the anticonvulsant drug valproate, and an oral compound formulated to prevent beta amyloid from binding to a specific brain receptor.

Many NIH-supported clinical trials for treating and slowing Alzheimer's disease are coordinated through the Alzheimer's Disease Cooperative Study (ADCS), which involves nearly 70 sites in the United States and Canada. In 2009, five new clinical trials were underway through the ADCS.

NIH actively is engaged in identifying gaps in Parkinson's disease research and developing programs to address them. Examples of progress include initiation of Phase III clinical trials of creatine and coenzyme Q10 to treat early Parkinson's disease; development of diagnostic criteria for depression and psychosis in people with Parkinson's disease; and support for a Parkinson's disease Gene Therapy Study Group. In 2009, a major clinical trial co-funded by NIH and the Department of Veterans Affairs published its finding that deep brain stimulation is more effective than standard drug therapy for Parkinson's disease but also carries higher risk of adverse events. NIH also supports 14 Morris K. Udall Centers for Excellence in Parkinson's Disease, which are identifying and characterizing disease-associated genes, examining neurobiological mechanisms, improving Parkinson's disease animal models, and developing and testing potential therapeutics. Three NIH Centers for Neurodegeneration Science also conduct research on Parkinson's disease. These centers will focus on gene-environment interactions, biomarkers to help identify people at risk, and mechanisms that may link exposure to toxic chemicals, such as agricultural pesticides, to increased susceptibility for Parkinson's disease.

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Aging is the most consistent risk factor for developing a neurodegenerative disorder, and many of the 50 million adults in the United States 60 years and older are at substantial risk for cognitive impairment and emotional disorders from many causes as they age. In addition, age-related cognitive decline distinct from dementia will affect most older individuals to some extent, with direct impacts on their independence and vitality. Although cognitive training, physical exercise, enhanced self-efficacy, social engagement, diet, environmental enrichment, and stress reduction all have been shown to have positive effects on cognition, the quality of the evidence varies widely across studies. NIH is partnering with the McKnight Brain Research Foundation through the Foundation for NIH to support the initial development and pilot testing of behavioral interventions that, individually and in combination, may remediate age-related cognitive decline.

Hearing and visual impairments also can result from degenerative processes. Tinnitus, the perception of ringing, roaring, clicking, or hissing sounds in the ears in the absence of an actual external sound source, is generally associated with age-related or noise-induced hearing loss. The neural basis of tinnitus remains poorly understood, and an NIH-supported study used brain imaging techniques for the first time in a rat model of tinnitus to identify brain regions affected by the condition. In other NIH-supported research, a recent examination of data from the National Health and Nutrition Examination Survey (NHANES) showed that hearing loss is about twice as common in adults with diabetes compared to those who do not have the disease. Diabetes may lead to hearing loss by damaging the nerves and blood vessels of the inner ear, disrupting blood flow to the inner ear, which is essential for normal hearing. NIH also supports research to

develop interventions to treat or prevent degenerative sensory impairments, such as efforts to protect against optic nerve damage associated with glaucoma, a major cause of blindness. Researchers recently showed in a mouse model of glaucoma that overexpressing the gene for a naturally occurring neuroprotective factor improved survival of neurons in the retina that make up the optic nerve.

NIH also supports research to develop interventions to treat or prevent degenerative sensory impairments, such as efforts to protect against optic nerve damage associated with glaucoma, a major cause of blindness.

Neurons are not unique in their vulnerability to degenerative disorders. Muscular dystrophies are a class of neuromuscular disorders that lead to progressive muscle weakness and degeneration. NIH support for research on muscular dystrophies includes funding for six Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (also see the section on *Wellstone Muscular Dystrophy Cooperative Research Centers* in Chapter 4), as well as targeted initiatives for translational research in neuromuscular disease. Multiple sclerosis is the most common of a number of diseases that lead to the degeneration of myelin, a fatty substance that ensheathes many nerve fibers in the brain. In 2007, a genome-wide association study with NIH support reported the first new genetic risk factors for multiple sclerosis to be identified in more than 20 years, and in 2009, meta-analyses and replication studies revealed additional new susceptibility genes. NIH also supports an ongoing randomized, double-blind, placebo-controlled Phase III trial (CombiRx) comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting multiple sclerosis. The trial will determine whether combination therapy offers an improvement over the partial efficacy of either of these commonly used medications. NIH intramural investigators are collaborating with this trial to identify biomarkers associated with different clinical and treatment response profiles.

Advancing Neuroscience Research through Collaboration

The melding of disciplines involved in the study of the nervous system and the overarching themes linking its many functions and disorders make neuroscience a naturally collaborative field of research. The NIH Blueprint for Neuroscience Research, a trans-NIH collaboration among 16 NIH ICs and Offices, catalyzes research progress by developing tools, research resources, and training opportunities that transcend the mission of any single NIH IC and serve the entire neuroscience community. Looking forward, the NIH Blueprint plans to support initiatives addressing Grand Challenges in the areas of pain research, mapping human brain connectivity, and therapy development for diseases of the nervous system. Further examples of collaboration in neuroscience research range from other joint activities across NIH ICs and Federal agencies, to data sharing and multisite networks in the research community, to coordinated efforts between NIH, extramural researchers, and those directly affected by disease to identify research needs and opportunities.

Looking forward, the NIH Blueprint for Neuroscience Research plans to support initiatives addressing Grand Challenges in the areas of pain research, mapping human brain connectivity, and therapy development for diseases of the nervous system.

Today's fast global communication, the power and storage capacity of modern computer systems, and advanced informatics tools are enabling collaborative research on increasingly large scales. NIH supports several data registries, databases, and tissue banks for neurological diseases and mental disorders that offer shared access to research resources, genetic and clinical data, and biological samples. For example, the National Database for Autism Research (NDAR)) is a collaborative biomedical informatics system created by NIH to house human genetic, imaging, and phenotypic data from research on ASD, and to make these data available to qualified researchers. In addition, through community-based development of a data dictionary, NDAR will foster a shared, common understanding of the complex data landscape that characterizes ASD research. The Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC), a NIH Blueprint program, provides information about and access to research tools and resources for the neuroimaging research community. In 2009, the NITRC received the "best overall" Excellence.gov award, the largest Federal award program to

recognize the very best in government information technology programs. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.)

NIH also facilitates collaborative approaches to research on disorders of the nervous system through many clinical and translational research networks and other programs that enable multisite studies. The Alzheimer's Disease Neuroimaging Initiative (ADNI), NIH's largest public-private partnership for brain research, is examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier, and with greater sensitivity, the development and progression of mild cognitive impairment and Alzheimer's disease. A recent ADNI study confirmed that changes in cerebrospinal fluid biomarkers may signal the onset of mild Alzheimer's disease and established a method and standard of testing for these biomarkers. The Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) supports a network of eight research centers established to develop acute stroke therapies from preclinical research through early-phase clinical trials. These centers also work to improve pre-hospital stroke care, participate in community education, and develop telemedicine to expand rapid access to acute stroke care. Additional NIH programs facilitate research on rare disorders, which would not be possible without a coordinated effort. For example, in 2009, NIH established the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC), a network of more than 200 community and academic practitioners for the study of risk factors, diagnosis, and treatments for neuro-ophthalmologic disorders such as idiopathic intracranial hypertension and ocular manifestations of Grave's disease, an autoimmune disorder. Several consortia funded through the NIH Rare Diseases Clinical Research Network (also see the section on *Rare Diseases Clinical Research Network* in Chapter 4) program focus on neurological disorders, including dystonia, brain vascular malformations, lysosomal storage disorders, and rare diseases of the autonomic nervous system.

The Alzheimer's Disease Neuroimaging Initiative, NIH's largest public-private partnership for brain research, is examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier, and with greater sensitivity, the development and progression of mild cognitive impairment and Alzheimer's disease.

NIH intramural investigators have worked with the Department of Defense and the Department of Veterans Affairs (VA) for many years on long-term neuropsychological outcomes of traumatic brain injury (TBI) in veterans. The high rate of TBI and post-traumatic stress disorder (PTSD) among military personnel returning from ongoing operations in Afghanistan and Iraq has led to expanded and new joint efforts with these and other agencies. Recent trans-agency workshops have focused on TBI classification, combination therapies for TBI, research opportunities and challenges for blast injury-induced TBI, and common data elements related to TBI and PTSD. In an ongoing collaborative effort with the U.S. Department of Defense Centers of Excellence and the VA to address the role of gender, race, and other socioeconomic factors on trauma spectrum disorders, NIH also has helped define directions for new interdisciplinary studies on the prevention, diagnosis, treatment, and management of TBI and PTSD, including a focus on their impact on families and communities and on increasing knowledge about women with TBI and PTSD.[27] In addition, the Center for Neuroscience and Regenerative Medicine (CNRM) is a newly established collaboration between the Uniformed Services University of the Health Sciences (USHUS) and the NIH Intramural Research Program for research on TBI. Projects within the center range from molecular and mechanistic studies to rehabilitation and outcomes research.

To identify research needs and opportunities, NIH relies strongly on the advice of the extramural research community, as well as on the important perspectives of people directly affected by disease. The NIH Epilepsy Research Benchmarks represent one of many examples of such collaborative activities across neuroscience to determine priority areas for research. The Benchmarks, first developed in 2000 and revised in 2007, reflect input from epilepsy researchers, physicians, patients, family members, and nonprofit organizations that support the epilepsy community and research efforts. NIH continues to collaborate with the broader epilepsy community to address the Benchmarks, including through a recent workshop on sudden unexplained or unexpected death in epilepsy (SUDEP), which focused on research needs to

understand and prevent SUDEP, and on improving awareness and education about SUDEP for patients, families, and health care providers.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Neurodevelopment: Periods of Growth, Maturation, and Vulnerability

Developmental Genomics: Neural tube defects are a class of birth defects affecting the brain and spinal cord. Taking folic acid during the weeks before and after conception greatly can reduce a woman's chances of having a child with a neural tube defect. Still, researchers have not yet fully defined the complex relationship that exists between folic acid and vitamin B12, which is essential for synthesizing DNA during growth and development. Because Ireland has a particularly high rate of neural tube defects, NIH researchers collaborated with Irish researchers to look more closely at the role of vitamin B12 in the developmental disorder. They found that children born to women who have low blood levels of vitamin B12 shortly before and after conception have an increased risk of a neural tube defect. In light of their discovery, researchers said it would be wise for all women of childbearing age to consume the recommended amount of vitamin B12 in addition to folic acid. In a study looking at a different type of birth defect, a trans-NIH team found that about 20 percent of the incidence of isolated cleft lip may be due to a very tiny alteration in a gene involved in facial development. Oral-facial clefts are among the most common birth defects in the United States, arising from disruptions in a dynamic but still poorly understood interplay of genes, diet, and environment.

→ Molloy AM, et al. *Pediatrics* 2009;123(3):917-23. PMID: 19255021.
Rahimov F, et al. *Nat Genet* 2008 Nov;40(11):1341-7. PMID: 18836445. PMCID: PMC2691688.
→ For more information, see http://www.genome.gov/27530477
→ For more information, see http://www.genome.gov/27528380
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Genomics*
→ (E, I) (**NHGRI**, NICHD, NIDCR)

The Collaborative Study on the Genetics of Alcoholism (COGA): In its 20th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) that are densely affected by alcoholism, enabling researchers to take a multigenerational perspective. A recent COGA study focusing on adolescents follows individuals longitudinally as they transition through the age of risk. Investigators have identified several genes, including *GABRA2, ADH4, ADH5, CHRM2, GRM8, GABRR1,* and *GABRR2* (*Rho 1* and *2*) that influence the risk for alcoholism and related behaviors, such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected, and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials

are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes that influence vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

- → Xuei X, et al. *Am J Med Genet B Neuropsychiatr Genet* 2009;150B(3):359-68. PMID: 19536785. PMCID: 2829340.
- → For more information, see http://zork.wustl.edu/niaaa
- → This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
- → (E) (**NIAAA**) (GPRA)

EARLI, the Early Autism Risk Longitudinal Investigation: EARLI, the Early Autism Risk Longitudinal Investigation, comprises a network of leading autism researchers from three regions across the country. EARLI is following a cohort of 1,200 mothers of children diagnosed with autism who are pregnant or planning a pregnancy. The EARLI network will study how genetics and environmental factors work together to cause autism by studying families who already are affected by autism. Data will be collected prospectively via clinical assessment, interviews, self-reports, medical record review, home environment assessments, and biologic samples that will be used in current analysis and stored for future studies. Planned analyses include a determination of whether in utero exposure to organic pollutants such as polychlorinated biphenyls (PCBs), brominated diphenyl ethers (BDEs), and persistent organic pollutants (POPs) is associated with autism risk.

- → For more information, see http://earlistudy.org
- → This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3*: Epidemiological and Longitudinal Studies*
- → (E) (**NIEHS**)

Addressing the Heterogeneity of Autism Spectrum Disorders: NIH released a series of Funding Opportunity Announcements (FOAs), supported by funds from the American Recovery and Reinvestment Act of 2009, soliciting applications for 2-year research projects to address the heterogeneity of Autism Spectrum Disorders (ASD). This initiative represents the largest NIH funding opportunity for research on ASD to date and will jump-start many of the short-term objectives set forth in the Interagency Autism Coordinating Committee's Strategic Plan for Autism Spectrum Disorder Research. The FOAs target research in areas such as measurement development, biomarkers, immune and central nervous systems interactions, genetics, environmental risk factors, model development, treatment and intervention, and services research.

- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-170.html
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-171.html
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-172.html
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-173.html
- → For more information, see http://www.nimh.nih.gov/science-news/2009/rising-to-the-challenge-nih-will-use-60-million-in-recovery-act-funds-to-support-strategic-autism-research.shtml
- → This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- → (E) (**NIMH**, NICHD, NIDCD, NIEHS, NINDS) (ARRA)

Insights into the Molecular Interplay Governing Formation of Cranial Sensory Ganglia: The developmental biology underlying sensory nerve development is fascinatingly intriguing. Take the trigeminal ganglion, which is responsible for touch, pain, and temperature sensation for most of the face. How do precursor cells self-organize in the embryo to produce an anatomically correct sensory network connecting to the central nervous system? Many of the answers are wired into the molecular circuitry of two transient embryonic cell types called neural crest cells and ectodermal placodes. They interact during embryonic development to differentiate into the nerve cells that form the trigeminal ganglion. But virtually nothing

is known about the molecular interplay that mediates this interaction. It is a biological puzzle with no known pieces. Now NIH grantees have introduced the first two pieces of the puzzle. They demonstrated in animal studies that the cranial subtype of neural crest cells express the protein Slit1 on their surface during their programmed migration to the trigeminal-forming ectodermal placodes. Meanwhile, as the trigeminal placode cells follow their developmental program, they express on their surface the Robo2 protein, which is the receptor for the Slit1 protein. The Robo2-Slit1 connection, like fitting a hand in a glove, mediates the interaction of neural crest and trigeminal placode cells during the formation of sensory ganglia. When the scientists disrupted one or both molecular signals, the resulting sensory ganglia were abnormal. The teams' findings are important to understanding the mechanisms that regulate formation of the sensory nervous system and thus provide potential targets for identifying the causes of congenital sensory disorders involving the neural crest cell population.

- → Shiau CE, et al. *Nat Neurosci* 2008;11(3):269-76. PMID: 18278043.
- → For more information, see http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/Archive/archive2008/April/TrigeminalGanglion.htm
- → For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18278043?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
- → This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
- → (E) (**NIDCR**)

Magnetic Resonance Imaging; Study of Normal Brain Development: Understanding healthy brain development is essential to finding the causes of many childhood disorders, including those related to intellectual and developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases. NIH is creating the Nation's first database of MRI measurements and analytical tools, and clinical and behavioral data to understand normal brain development in approximately 500 children from across the Nation. This large-scale longitudinal study uses several state-of-the-art brain-imaging technologies. Anatomical neuroimaging scans; demographic, medical, cognitive, and behavioral data; and magnetic resonance spectroscopy data now are available to the research community via the NIH MRI Study of Normal Brain Development website.

- → For more information, see http://www.bic.mni.mcgill.ca/nihpd/info/index.html
- → This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- → (E/I) (**NICHD**, NIDA, NIMH, NINDS) (GPRA)

Brain Matures a Few Years Late in ADHD: NIH-supported research on brain development in children with attention-deficit/hyperactivity disorder (ADHD) showed a normal pattern of brain development, but with a striking delay in cortical maturation. Between ages 5 and 15, the maturation of the prefrontal cortex was found to be delayed by roughly 3 years in children with ADHD compared to age-matched children without the disorder. Current studies now are exploring the effects of treatment on the rate of cortical maturation.

- → Shaw P, et al. *Proc Nat Acad Sci U S A* 2007;104(49):19649-54. PMID: 18024590. PMCID: PMC2148343.
- → For more information, see http://www.nimh.nih.gov/science-news/2007/brain-matures-a-few-years-late-in-adhd-but-follows-normal-pattern.shtml
- → This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- → (I) (**NIMH**)

The Role of Development in Drug Abuse Vulnerability: NIH supports animal, clinical, and epidemiological research across the lifespan to examine how developmental stage may influence drug abuse vulnerability or protection. The discovery of a protracted period of brain changes during early development and beyond has been critical to understanding

the role of brain maturation in decision-making processes and responses to stimuli, including early (e.g., in utero) exposure to drugs. Adolescence has emerged as a particularly vulnerable period, during which an immature brain circuitry can translate into a preponderance of emotional reactivity (vs. higher cognitive control) that gives rise to the impulsive characteristics of many teenagers. This in turn may lead to dangerous risk-taking, such as experimenting with drugs that ultimately can lead to addiction. Using both animal models and clinical research, scientists are beginning to understand how environmental variables can play a key role in shaping brain maturation trajectories. In this regard, imaging, genetic, and epigenetic tools are helping interpret the effects of myriad environmental influences, such as quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics on brain development and behavior. In addition, the field of social neuroscience is harnessing the power of multidisciplinary approaches to tease apart these multilevel phenomena to better understand, for example, the neural mechanisms of peer pressure, the connections between chronic stress and risk of drug abuse initiation, and the impact that different early rearing environments can have on gene expression and behavior.

→ For more information, see http://www.nida.nih.gov/tib/prenatal.html
→ For more information, see http://www.nida.nih.gov/scienceofaddiction/
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDA**, NICHD) (GPRA)

Preventing Drug Abuse in Children and Adolescents: Intervening early to reduce risk factors for drug abuse and related problem behaviors can have tremendous impact and improve the trajectory of a young life. NIH is using a multipronged approach to achieve more effective substance abuse prevention by: (1) developing novel strategies, (2) exploring long-term and crossover effects of proven programs, and (3) improving adoption and implementation of evidence-based approaches. Innovative ideas being explored include physical activity to counter drug use, interactive Web-based technologies to engage young people, and brain imaging results to better target media messages. NIH also is building on proven methods such as universal prevention programs, which can reduce an array of risk behaviors, including substance abuse. These programs typically target behaviors appropriate to a child's developmental stage and have been shown to achieve long-term effects. For example, fifth graders who participated in the school-based prevention program "Positive Action" as first graders were about half as likely to engage in substance abuse, violent behavior, or sexual activity as those who did not. Similarly, exposure to the "Good Behavior Game," designed to reduce aggressive, disruptive behavior in first and second grade classrooms, led to fewer drug and alcohol disorders, lower rates of regular smoking, less antisocial personality disorder, and reduced delinquency and violent crime in young adults. However, the development of evidence-based prevention programs is meaningless unless they are adopted by communities. Therefore, NIH also is striving to increase implementation of successful prevention approaches in U.S. schools and communities.

→ Beets MW, et al. *Am J Public Health* 2009;99(8):1-8. PMID: 19542037.
Kellam SG, et al. *Drug Alcohol Depend* 2008;95 Suppl 1:S5-S28. PMID: 18343607. PMCID: PMC2512256.
Spoth R, et al. *Am J Prev Med* 2007;32 (5):395-402. PMID: 17478265.
→ For more information, see http://www.nida.nih.gov/scienceofaddiction/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**)

Underage Drinking Research Initiative: In 2004, NIH launched its Underage Drinking Research Initiative with the goal of obtaining a more complete and integrated scientific understanding of the environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence—all framed within the context of overall human development. Activities and accomplishments in 2008 and 2009 include: (1) working with the Office of the Surgeon General to disseminate *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking*, including state roll-outs in

Oklahoma, Ohio, Nebraska, Wyoming, Montana, Maryland, and Rhode Island (in addition to the six held in 2007); (2) continuing to convene scientific meetings of experts to advance underage drinking research. A series of meetings focusing on the development of guidelines and recommendations for screening children and adolescents for risk for drinking, alcohol abuse, and alcohol use disorders continued in 2008-2009; (3) issuing RFAs and program announcements (PAs), including "Limited Competition: Underage Drinking: Building Health Care System Responses (Phase II)" (RFA-AA-09-001) and "Alcohol, Decision-Making, and Adolescent Brain Development" (PA- 09-097 (R01) and PA-09-096 (R21)); (4) published "A Developmental Framework for Underage Alcohol Use;" and (5) published a *Pediatrics* supplement of seven developmentally focused papers covering a broad range of underage drinking topics.

→ A Developmental Perspective on Underage Alcohol Use. *Alcohol, Research and Health* 2009;32(1). Available at: http://pubs.niaaa.nih.gov/publications/arh321/toc32-1.htm.
Masten AS, et al. *Pediatrics* 2008;121 Suppl 4:S235-51. PMID: 18381492. Available at: http://pediatrics.aappublications.org/cgi/reprint/121/Supplement_4/S235.
→ For more information, see http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E, O) (**NIAAA**)

Neuroplasticity: Substrates for Change and Repair

Advances in Mental Health Treatment Development: NIH continues to fund research into the development of targeted medications and treatments for mental disorders.

- *Novel NeuroAIDS Therapies:* Integrated Preclinical/Clinical Program (IPCP): The IPCP supports drug development efforts focused on new targets that may modulate immune responses and protect brain cells in the context of HIV infection. One NIH-supported group will develop the use of nanotechnology to enhance delivery of HIV drugs to the brain. Another research group will investigate the therapeutic potential of various compounds to treat or prevent HIV-associated mental disorders.
- *Innovative Approaches to Personalizing the Treatment of Depression:* NIH will advance research on individualizing the treatment of depression by supporting efforts to develop models and test new approaches that, by accounting for patient characteristics, aim to be more specific and thus potentially lead to more effective and efficient treatment interventions. Several studies will be supported through this initiative.
- *Fast-Acting Depression Treatments:* Previous NIH-funded research found that ketamine can lift depression in just hours, instead of the weeks it takes conventional antidepressants. NIH researchers now have identified a marker that predicts a patient's response using the split-second accuracy of magentoencephalography. Depressed patients showed increased activity in the anterior cingulate cortex (ACC; a region found in brain imaging studies to signal better treatment responsiveness) that correlated with their response to ketamine while viewing certain visual stimuli. This ACC activity may indicate the dysfunctional workings of the brain circuit that is targeted by ketamine.

→ Salvadore G, et al. *Biol Psychiatry* 2009;65(4):289-95. PMID: 18822408. PMCID: PMC2643469.
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-040.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-010.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIMH**)

Clinical Trials Networks for the Treatment of Mental Disorders: NIH is using its extensive clinical trials networks as platforms for investigating effective treatments for mental disorders. The networks, which are maintained through infrastructure supported by NIH, evolved from a recent series of practical clinical trials. The networks comprise more than 60 sites throughout the United States that maintain continual outreach efforts to diverse groups of patients and families with mental illnesses. The Bipolar Trials Network is conducting the Lithium Use for Bipolar Disorder (LiTMUS) trial,

which will study the use of moderate-dose lithium for the treatment of bipolar disorder among 264 participants. The Depression Trials Network is seeking participants for the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. This study will examine for the first time whether two different medications, when given in combination as the first treatment step, compared to one medication, will enhance remission rates, increase speed of remission, be tolerable to the participant, and provide better sustained benefits in the longer term. Results of this study, involving 660 participants, will inform practitioners in managing the treatment of patients with chronic or recurrent depression.

- → For more information, see http://www.clinicaltrials.gov/show/NCT00667745
- → For more information, see http://www.clinicaltrials.gov/show/NCT00590863
- → This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- → (E) (**NIMH**)

New Genetics/Epigenetic Tools Shed Light on Addiction: NIH-supported research is taking full advantage of expanding databases and fast technologies to identify links between genetic variations and disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms underlying complex diseases like addiction, which genes strongly influence. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as “gene chips” (e.g., the neurexin gene has been found to play a role in drug addiction). Applying these tools to addiction and other brain disorders advances our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient's genetic profile. To complement these efforts, NIH is investing in the equally important field of epigenetics, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the deleterious long-term changes to brain circuits from drug abuse. For example, using a powerful new technique known as ChIP-on-chip to monitor epigenetic changes correlated with gene activity, investigators recently have mapped the genomic effects of chronic cocaine use in the reward center of the mouse brain. Such analyses provide needed information about which genes are altered by cocaine and can point to new targets for medications development. Epigenetic discoveries also can inform ways to smartly alter environmental factors so as to decrease the risk for drug abuse and addiction.

- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-015.html
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-016.html
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-003.html
- → For more information, see http://nihroadmap.nih.gov/epigenomics/initiatives.asp
- → For more information, see http://nihroadmap.nih.gov/commonfundupdate.asp
- → This example also appears in Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- → (E/I) (**NIDA**, NCI, NIAAA, NIMH) (GPRA)

Genes Involved in the Regulation of Sensitivity to Alcohol: Low doses of alcohol are stimulating in both humans and animals while higher doses have sedating effects. Sensitivity to alcohol, however, varies across individuals and low sensitivity to alcohol is a risk factor for the development of alcohol dependence in humans. Research with individuals who have a high family history of alcoholism seeks to understand how low response to alcohol contributes to dependence and how it can be used to predict risk for future alcohol problems. Research with animals is useful in identifying the mechanism(s) underlying the level of sensitivity to alcohol. Recently, a study with fruit flies implicated the Epidermal Growth Factor Receptor (EGFR) signaling pathway in regulating sensitivity to alcohol. Importantly, FDA-approved medications that inhibit EGFR increase alcohol sensitivity in mice and decrease alcohol intake in rats, suggesting that these drugs may offer therapeutic opportunities for treatment of alcohol use disorders in humans.

→ Corl AB, et al. *Cell* 2009;137(5):949-60. PMID: 19464045.
Trim RS, et al. *Alcohol Clin Exp Res* 2009;33(9):1562-70. PMID: 19485971.
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIAAA**)

Chemical Messengers in the Brain Determine the Response to Stress and Regulate Craving For Alcohol: Stress contributes to many disease states, including alcohol dependence. As alcohol dependence evolves, stress systems in the brain play an increasing role in continued alcohol use and relapse. Furthermore, individuals differ widely in response to stress. NIH researchers have investigated specific chemical messengers in the brain and the roles these messengers play as mediators of behavioral stress responses and their contributions to alcohol dependence. For example, the chemical messenger neuropeptide Y (NPY) is expressed in regions of the brain implicated in arousal and in determining emotional states. Production of NPY increases in these brain regions in response to emotionally charged and stressful conditions. Higher levels of NPY are associated with lower levels of alcohol consumption. NIH researchers also have made progress in studies of another brain messenger involved in stress responses, Neurokinin 1 (NK1) and its receptor (NK1R). In a clinical study, alcohol-dependent inpatients who recently stopped drinking were treated with a drug that blocks the actions of NK1R. Patients treated with the NK1R blocker exhibited reduced alcohol cravings, improved overall well-being, and reduced blood levels of stress hormones. Brain imaging during responses to stimulation that increases the likelihood of drinking showed a beneficial effect by the drug, suggesting that such drugs could reduce relapse in alcohol-dependent individuals.

→ Zhou Z, et al. *Nature* 2008;452(7190):997-1001. PMID: 18385673. PMCID: PMC2715959.
George DT, et al. *Science* 2008; 319(5869):1536-9. PMID: 18276852.
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E/I) (**NIAAA**)

Programs to Accelerate Medication Development for Alcoholism Treatment: Alcohol dependence is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ among individuals. Therefore, a diverse repertoire of medications is needed to provide effective therapy to a broad spectrum of alcohol-dependent individuals. Although promising compounds have been identified, developing medications is a long and costly process with a low probability of success for any single agent. NIH has initiated collaborations with the pharmaceutical industry to ensure its interest in taking promising compounds through the final phase of clinical trials and subsequent FDA consideration. As part of this approach, two new programs have been initiated:

- Laboratories have been established to screen promising compounds with animal models, enabling faster determination of those that merit advancement to large, multisite studies. Animal studies already have produced several targets for human studies that now are underway. The animal models are being validated using medications that have been tested clinically.
- A network of sites is being developed to conduct early Phase II proof-of-concept human trials. NIH will encourage the pharmaceutical industry to screen proprietary compounds in the preclinical models and, when results are positive, test them in the early Phase II human trials network. Currently quetiapine and levetiracetam are being evaluated in this network.
- Pharmacogenetic studies are ongoing to determine genetic variants that predict success for various medications.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAAA**) (GPRA)

A Multidisciplinary Approach to Tobacco Addiction: Tobacco addiction is the number one preventable public health threat, with enormous associated morbidity, mortality, and economic costs. Cigarette smoking—powerfully addictive mainly because of the key ingredient nicotine—is the greatest preventable cause of cancer, accounting for at least 30 percent of all cancer deaths, 87 percent of lung cancer deaths, and nearly 80 percent of deaths from chronic obstructive pulmonary disease, according to CDC. CDC also reports that these leading causes of death could become relatively uncommon in future generations were the prevalence of smoking substantially reduced. In that vein, NIH-supported research has led to major advances in critical areas that together could greatly enhance our ability to either prevent or mitigate the impact of tobacco addiction. Convergent genomic studies recently have uncovered several genes previously not associated with nicotine reward or addiction that convey increased risk for addiction. This finding identifies markers of vulnerability, as well as new targets for medications development, with the potential to personalize, and thereby improve, treatment based on patients' genetic profiles. Clinical trials are exploring new medications and behavioral therapies for tobacco addiction. A promising approach, which already completed Phase II clinical testing, is that of immunotherapy. A nicotine vaccine (NicVAX), which binds nicotine in the blood, preventing it from ever reaching the brain, showed strong positive results in promoting abstinence among study participants who achieved sufficient antibody levels. Further studies are helping to define optimal protocols for vaccination to improve results in all smokers. This may be a particularly useful tool for tobacco cessation programs in the not-too-distant future.

→ Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and productivity losses United States, 1997-2001. *Morb Mortal Wkly Rep* 2005;54:625-8.
Centers for Disease Control and Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses United States, 2000-2004. *Morb Mortal Wkly Rep* 2008;57(45):1226-28.
Institute of Medicine. *Ending the Tobacco Problem: A Blueprint for the Nation.* Washington, DC: National Academies Press; 2007.
→ For more information, see http://www.drugabuse.gov/ResearchReports/Nicotine/Nicotine.html
→ For more information, see http://cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDA**, NCI) (GPRA)

Transdisciplinary Tobacco Use Research Centers—Alcohol Use and Smoking: Multiple Institutes at NIH are co-funding seven collaborative, transdisciplinary centers to identify familial, early childhood, and lifetime psychosocial pathways related to smoking initiation, use, cessation, and patterns of dependence. Research on genetics of addiction, physiological biomarkers, and the use of advanced imaging techniques can lead to individualized and community approaches for tobacco prevention and treatment. This model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships. Some recent highlights include: For smokers quitting while taking the prescription drug bupropion, the risk of smoking relapse was associated primarily with heavy, rather than with moderate drinking. Interactions between brain pathways activated by nicotine and alcohol may increase the likelihood of drinking in humans who simultaneously smoke and drink, suggesting that drugs that block nicotinic receptors also may help to reduce drinking. Varenicline, an agonist of certain nicotinic acetylcholine receptors, is a smoking cessation medication that has been shown in preclinical research to reduce alcohol drinking. Researchers are testing varenicline in preclinical models of ethanol drinking to determine which nicotinic receptor subtypes are most important. Recently, they found that varenicline reduces alcohol self-administration in heavy-drinking smokers.

→ For more information, see http://dccps.nci.nih.gov/tcrb/tturc
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIAAA**, NCI, NIDA)

The Critical Need for Addiction Medications: Breakthrough discoveries in the last decade have led to a profound transformation in understanding the mechanisms and consequences of drug abuse and addiction. The current picture offers a unique opportunity for the results of NIH's collective research to be translated into new, effective pharmacotherapies that could, either by themselves or with tested behavioral treatments, help alleviate the devastating personal and societal impacts of addiction. Distinct from the process that occurs with many other diseases, medications development for addiction suffers from minimal pharmaceutical industry involvement—likely because of real or perceived financial disincentives and stigma. Thus, despite many enticing scientific leads, we still have no medications available for stimulant, cannabis, inhalants, or polysubstance abuse, a gap that NIH is attempting to fill. Current efforts are capitalizing on a greater understanding of the neurobiology underlying addiction and of newly identified candidate systems and molecules. Several innovative treatment approaches—beyond targeting the brain's reward system—have proven feasible and are progressing to more advanced stages of research and development. Projects in this context include work on medications to diminish conditioned responses, promote new learning, and inhibit stress-induced relapse. In addition, vaccines (e.g., for nicotine, cocaine) are being developed that induce the body to produce drug-specific antibodies able to sequester drug molecules while they are still in the bloodstream and prevent them from entering the brain. Next-generation pharmaceuticals also will emerge from human genome studies uncovering novel targets for better tailoring of treatments according to a person's genes.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**) (GPRA)

Neurobiology of Appetite Control: NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. For example, the sight of food has been found to induce different responses in the brains of patients following weight loss; these differences are due to changes in levels of the hormone leptin. Researchers also discovered that rats susceptible to becoming obese from a high-calorie diet have fewer neural connections in the brain in the hypothalamus (the part of the brain that has a key role in weight regulation) compared to normal rats. Additionally, a factor secreted by the small intestine in response to dietary fat intake has been found to enter the brain and suppress appetite in rats. More recently, six new genetic regions associated with obesity were identified and found to be in or near genes expressed in the brain. To highlight further the connection between brain function and obesity, a trans-NIH workshop on neuroimaging in obesity research was held to share data and experiences with functional neuroimaging approaches to study brain involvement in various aspects of obesity such as weight gain and loss, and the neurotransmitters and brain structures associated with energy balance, hunger, and decision-making. A recent funding opportunity announcement was issued to foster new research using neuroimaging approaches to enhance understanding of food intake and energy expenditure in the context of obesity. This research has implications for new therapies for obesity.

→ Rosenbaum M, et al. *J Clin Invest* 2008;118(7):2583-91. PMID: 18568078. PMCID: PMC2430499.
Bouret SG, et al. *Cell Metab* 2008;7:7(2):179-85.PMID: 18249177. PMCID: PMC2442478.
Gillum MP, et al. *Cell* 2008;135(5):813-24.PMID: 19041747. PMCID: PMC2643061.
Willer CJ, et al. *Nat Genet* 2009;41(1):25-34. PMID: 19079261. PMCID: PMC2695662.
→ For more information, see http://www3.niddk.nih.gov/fund/other/neuroimaging2008/
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/rfa-dk-08-009.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDDK**)

Understanding the Roles of Non-Neuronal Cells in Neuropathic Pain Provides New Targets for Intervention: Chronic pain caused by nerve injury, called neuropathic pain, is difficult to treat because we do not yet fully understand the biological mechanisms underlying its development and persistence. Most pain-relieving medications for chronic pain target nerve cells, yet it is becoming clear that non-nerve (non-conducting) cells also play an important role in

some chronic pain conditions. Matrix metalloproteases (MMPs) are enzymes that break down the medium surrounding tissue cells. MMPs also activate several pro-inflammatory proteins that stimulate the non-nerve conducting function of of the supportive glial cell. Scientists are wondering if neuropathic pain and inflammation are linked by a common mechanism involving MMP activation. Researchers found that a specific matrix metalloprotease, MMP9, showed increased activity soon after nerve injury, which stimulated the glial cells in the spinal cord, but this increased activity declined after several days. A different enzyme, MMP2, also was increased, but at later times after injury; this increase led to activation of another nerve-supportive cell in the spinal cord. The research showed that the pain response of nerve-injured animals were blocked early by inhibitors of MMP9 or later by inhibitors of MMP2. These findings suggest an important role for MMP9 in the onset of chronic neuropathic pain conditions, and for MMP2 in the persistence of those conditions. The results also demonstrate the complex interplay between nerve cells and several non-nerve cells. This research describes a novel set of molecules involved in neuropathic pain, and points scientists toward new targets for possible interventions to short-circuit the onset and persistence of chronic pain conditions.

→ Kawasaki Y, et al. *Nat Med* 2008;14(3):331-6. PMID: 18264108. PMCID: PMC2279180.
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDCR**)

Promising Approaches to Treating Chronic Pain: Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can result in addiction, tolerance, and physical dependence, all of which may undercut their value in some patients. Thus, an area of enormous need is the development of potent analgesics with diminished abuse liability for treating chronic pain. In response, NIH has implemented an aggressive and multidisciplinary research program that is yielding tangible results, which stand to revolutionize the field of pain management. At the molecular level, cannabinoid (CB) research has shown that it is possible to activate the CB system selectively to provide analgesia with minimal or no effects on mental function, and no abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different (heteromeric) receptors. Targeting them could provide a vastly expanded range of pharmacotherapeutics. This approach has already ushered in the development of promising designer molecules that can block pain more selectively and safely. At the cellular level, active research on non-neuronal brain cells has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their proinflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of other analgesic drugs. At the brain circuit level, a new approach has been developed to harness the brain's intrinsic capacity to train itself through a strategy in which subjects “learn” how to regulate pain by viewing, and then controlling, images of their own brains in real time.

→ Varga EV, et al. *Curr Mol Pharmacol* 2008;1(3):273-84. PMID: 20021440.
Ferre S, et al. *Trends Neurosci* 2007;30(9):440-6. PMID: 17692396.
Daniels DJ, et al. *Proc Natl Acad Sci U S A* 2005;102(52):19208-13. PMID: 16365317. PMCID: PMC1323165.
Ledeboer A, et al. *Expert Opin Investig Drugs* 2007;16(7):935-50. PMID: 17594181.
deCharms RC. *Trends Cogn Sci* 2007;11(11):473-81. PMID: 17988931.
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDA**, NINDS)

Bioactive Nanostructures for Neural Regeneration: Spinal cord injury (SCI) often leads to permanent paralysis and loss of sensation below the site of injury because of the inability of damaged axons to regrow across the injury site in adults. Nanomaterials built from a family of self-assembling molecules may offer hope for treating serious injuries, such as spinal cord injury according to new results from NIH research. Recently, an NIH-supported research group developed peptide amphiphile (PA) molecules that self-assemble in vivo into supramolecular nanofibers and tested them on mouse models of spinal cord injury. In this work, in vivo treatment with the PA nanofibers, after SCI, reduced cell death and promoted

regeneration of both motor fibers and sensory fibers through the lesion site. Treatment with the PA also resulted in significant behavioral improvement. These observations demonstrate that it is possible to inhibit glial scar formation and to facilitate regeneration after SCI using bioactive three-dimensional nanostructures displaying high densities of neuroactive epitopes on their surfaces.

→ Tysseling-Mattiace VM, et al. *J Neurosci* 2008;28(14):3814-23. PMID: 18385339. PMCID: PMC2752951.
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*
→ (E) (**NIBIB**)

Neural Interfaces Program: Neural interfaces are systems that operate at the intersection of the nervous system and an internal or external device, including neural prosthetics. Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. NIH pioneered the development of this technology, beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants, which help people with hearing impairments; respiratory and hand grasp devices for people with spinal cord injuries; and deep brain stimulation for Parkinson's disease, among other contributions. Current work aims to restore voluntary bowel and bladder control and standing to spinal cord-injured persons, allow paralyzed persons to control devices directly from their brains, improve cochlear implants, and improve deep brain stimulation, which may be applicable to many brain disorders. Through the years, the program has fostered the development of a robust research community, now including private sector companies, and represents a cooperative effort among several ICs, which also coordinate their efforts with programs that now are underway in the Department of Veterans Affairs and Department of Defense.

→ For more information, see http://www.ninds.nih.gov/funding/research/npp/index.htm
→ For more information, see http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*
→ (E) (**NINDS**, NEI, NIBIB, NICHD, NIDCD)

Stem Cell Studies Provide Foundation for Possible Future Hearing Loss Treatments: Tiny cells inside your ear, known as hair cells, detect the vibrations in the air that constitute sound and turn them into electrical impulses that are sent to the brain. In mammals, when hair cells are damaged, the ability to detect sound is lost or compromised because hair cells cannot be replaced. Once the hair cells are lost, the sensory cells that are next in the relay of sound information, known as spiral ganglion neurons (SGNs), also are at risk of dying due to lack of input. Scientists are working to replace lost or damaged hair cells and their SGNs in the hope of restoring lost hearing. NIH-supported scientists discovered that a specific population of cells from the inner lining of the adult mouse brain (ependymal cells), which arise during development from the same part of the brain that produces hair cells, are capable of dividing and share important similarities with hair cells. This population of cells also is found in the adult human brain. In related studies, the scientists also isolated mouse neural stem cells (NSCs) that are capable of differentiating into neurons that exhibit SGN-like properties. When cocultured with mouse SGNs, both NSCs and ependymal cells formed active connections with the SGNs. This research suggests that stem cells isolated from an adult brain may be able to replace lost inner-ear sensory cells and the neurons that connect these cells to the brain. These findings may provide a foundation for future treatments for hearing loss.

→ Wei D, et al. *Proc Natl Acad Sci U S A* 2008;8-9. PMID: 19064919. PMCID: PMC2634930.
→ (E) (**NIDCD**)

Neurodegeneration: Fighting the Effects of Age, Exposure, and Disease

Translational Research on Alzheimer's Disease (AD): To move basic research on AD and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. A number of agents are undergoing testing, including antihypertensives, anti-inflammatory drugs, and novel small molecules. In addition, in recent years, NIH-supported basic research has contributed to industry development of new Alzheimer's disease drugs. This program is a cornerstone of the NIH GPRA goal to "by 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

- → For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-048.html
- → This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
- → (E) (**NIA**) (GPRA)

Grape Seed Extract May Help Neurodegenerative Diseases: Tauopathies—a group of neurodegenerative conditions such as Alzheimer's disease—have been linked to the build-up of "misfolded" tau proteins in the brain. (Tau proteins are associated with microtubules, which help to regulate important cellular processes.) In light of previous studies indicating that grape-derived polyphenols may inhibit protein misfolding, an NIH-funded research center examined the potential role of a particular grape seed polyphenol extract (GSPE) in preventing and treating tau-associated neurodegenerative disorders. In one study, the researchers found that this GSPE reduced Alzheimer's-type neuropathology and cognitive decline in a mouse model of Alzheimer's disease and inhibited an Alzheimer's-linked process called cerebral amyloid deposition. In another study, the researchers used a variety of analytical techniques to clarify further how the GSPE produces its effects. The results of their preclinical study showed that GSPE interferes with the generation of tau protein aggregates and also disassociates preformed aggregates. Thus, GSPE may affect processes critical to the onset and progression of neurodegeneration and cognitive dysfunctions in tauopathies. The studies' findings, together with indications that this GSPE is likely to be safe and well-tolerated in people, support further exploration and development of GSPE as a therapy for Alzheimer's disease.

- → Ho L, et al. *J Alzheimers Dis* 2009;16(2):433-9. PMID: 19221432. PMCID: PMC2800939.
  Ono K, et al. *J Biol Chem* 2008;283(47):32176-87. PMID: 18815129. PMCID: PMC2583320.
  Wang J, et al. *J Neurosci* 2008 Jun 18;28(25):6388-92. PMID: 18562609. PMCID: PMC2806059.
- → For more information, see http://nccam.nih.gov/research/results/spotlight/031209.htm
- → This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- → (E) (**NCCAM**)

Alzheimer's Disease Cooperative Study (ADCS): Much of the AD-related clinical research supported by NIH takes place through the ADCS. The study involves a consortium of centers in the U.S. and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of AD or predict development of the disease in vulnerable people. To date, approximately 4,600 people have participated in the trials. Five new trials are underway through ADCS. These include: (1) a trial to examine whether treatment with DHA, an omega-3 fatty acid, will slow decline in AD; (2) a multicenter trial to evaluate home-based assessment methods for AD prevention research in people age 75 or older; (3) a trial to evaluate the efficacy and safety of 18 months of treatment with the drug PF-04494700 (TTP488), an oral compound formulated to prevent amyloid beta from binding to a specific brain receptor; (4) a trial of valproate, an anticonvulsant drug, to determine its ability to delay the emergence of agitation and psychosis and possibly the clinical progression of AD; and (5) a trial of intravenous immunoglobulin, which contains naturally occurring antibodies against beta-amyloid, to establish its clinical utility for treating AD. This program is a cornerstone of the NIH

GPRA goal to: "By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

→ For more information, see http://www.adcs.org/Default.aspx
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIA**) (GPRA)

Ginkgo Evaluation of Memory (GEM) Study Shows No Benefit in Preventing Dementia in the Elderly: Dementia is a loss of brain function that causes serious changes in memory, personality, and behavior. Alzheimer's disease, the most common form of dementia in older people, affects as many as 4.5 million Americans. Some people use extracts of leaves from the *Ginkgo biloba* tree in an effort to prevent or treat Alzheimer's and other types of dementia. NIH-supported researchers tested ginkgo in a large sample of older adults to see whether it could prevent or delay the onset of dementia, particularly Alzheimer's. The study enrolled 3,069 participants ages 75 or older who had normal cognition or mild cognitive impairment. For about 6 years, they took twice-daily doses (120 milligrams) of either ginkgo extract or a placebo. The study found that ginkgo did not lower the overall incidence of dementia or Alzheimer's. Nevertheless, the study demonstrates the feasibility of large dementia prevention trials in older adults, and provides useful information about how to design and conduct such trials. The results of this study confirm the importance of randomized trials in determining therapeutic benefit of new approaches to dementia and Alzheimer's disease. The results also provide a wealth of information that will be valuable in designing future clinical trials. Future analyses of the data will provide additional information on ginkgo's possible effects on cardiovascular disease, cancer, depression, and other age-related conditions. They also may identify subgroups at greater risk for developing dementia.

→ Kinlock TW, et al. *J Subst Abuse Treat* 2009;37(3):277-85. PMID: 19017911. PMCID: PMC2823569.
→ For more information, see http://nccam.nih.gov/research/results/gems/
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NCCAM**, NHLBI, NIA, NINDS, ODP/ODS)

Progress in Parkinson's Disease Research: For the past 7 years, NIH actively has been engaged in identifying gaps in Parkinson's disease research and developing programs to address them. Examples of progress include initiation of Phase III clinical trials of creatine and coenzyme Q10 to treat early Parkinson's disease; development of diagnostic criteria for depression and psychosis in people with Parkinson's disease; and support for a Parkinson's disease Gene Therapy Study Group. In 2009, a major clinical trial co-funded by NIH and the Veterans Administration published its finding that Deep Brain Stimulation is more effective than standard drug therapy for Parkinson's disease but also carries a higher risk of adverse events. NIH also has begun to formally assess the effectiveness of its programs by completing an evaluation of its Morris K. Udall Centers of Excellence in Parkinson's Disease Research. This evaluation included an assessment of scientific progress made by the centers and the value of using a centers mechanism, as well as an exploration of the effectiveness of program management and review in supporting the centers. The Working Group tasked with this evaluation released its findings in September 2007.

→ Weaver FM, et al. *JAMA* 2009;301(1):63-73. PMID: 19126811.
→ For more information, see http://www.ninds.nih.gov/funding/research/parkinsonsweb/index.htm
→ For more information, see http://www.parkinsontrial.ninds.nih.gov/index.htm
→ For more information, see http://www.ninds.nih.gov/news_and_events/press_releases/pressrelease_creatine_03222007.htm
→ For more information, see http://www.ninds.nih.gov/udall_centers_evaluation
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NINDS**)

Centers for Neurodegenerative Science: NIH has awarded three Centers for Neurodegeneration Science program grants to conduct research that combines human studies with basic mechanistic research to understand how environmental factors

contribute to the origins, progression, treatment, and prevention of neurodegenerative diseases. The three projects will focus on investigating Parkinson's disease (PD). PD is linked to pesticide exposure, mitochondrial damage, and altered storage of dopamine. One project will look at how environmental and genetic factors interact in PD pathogenesis and search for biomarkers that will help identify people at risk for developing PD. A second project will investigate the importance of the ubiquitin-proteasome system, microtubules, and aldehyde dehydrogenase disruption by pesticides in conferring vulnerability to dopamine neurons. An integrated, multidisciplinary approach will be used to identify agricultural pesticides that are able to disrupt the same cellular pathways shown to alter the viability of dopaminergic neurons and determine whether these pesticides increase the risk of PD. The third project will focus on proteins known to be related to PD with the goal of determining how chemical reactions lead to damaging modifications of these proteins. Clinical implications will be explored through biomarker development and a screen to identify compounds that can preserve protein function by reducing free radical stress. The knowledge generated by these projects will provide therapeutic targets for disease intervention and prevention strategies.

→ Yu T, et al. *Bioinformatics* 2009;25(15):1930-6. PMID: 19414529. PMCID: PMC2712336.
Orr AG, et al. *Nat Neurosci* 2009;12(7):872-8. PMID: 19525944. PMCID: PMC2712729.
Taylor TN, et al. *J Neurosci* 2009;29(25):8103-13. PMID: 19553450. PMCID: PMC2813143.
Guillot TS, Miller TW. *Mol Neurobiol* 2009;39(2):149-70. PMID: 19259829.
Cho DS, et al. *Science* 2009;324(5923):102-5. PMID: 19342591. PMCID: PMC2823371.
Xiong H, et al. *J Clin Invest* 2009;119(3):650-60. doi: 10.1172/JCI37617. PMID: 19229105. PMCID: PMC2648688.
Choo YS, Zhang Z. *J Vis Exp* 2009 Aug 19;(30). pii: 1293. doi: 10.3791/1293. PMID: 19692941.
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIEHS**)

New Indications for Established Agents to Treat Chronic Disease: When identifying interventions to treat an illness or chronic condition, testing drugs that already have been developed for other conditions sometimes can be faster and more cost-effective than designing entirely new agents because drug safety profiles already have been established, and contraindications already are known. NIH intramural investigators currently are exploring the use of several established agents in the treatment of chronic disease. For example, a growing body of animal research suggests that the compound fenoterol, widely used for treatment of pulmonary disease, may be effective in the treatment of congestive heart failure. Experimental results with fenoterol are sufficiently encouraging to recommend advancing translational efforts and planning clinical trials. Other studies in animal models have shown that the drug erythropoietin, used to treat certain types of anemia, has a protective effect on the heart if administered shortly after a heart attack. Based on the results of these studies, researchers have initiated a study to assess the effects of erythropoietin (EPO) on the heart after a heart attack. Researchers also have reported preclinical data that suggest a therapeutic benefit of the diabetes drug exendin-4 in the treatment of stroke and Parkinson's disease.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (I) (**NIA**)

Interventions to Remediate Age-Related Cognitive Decline: Age-related cognitive decline distinct from dementia will affect most older individuals to some extent and has a direct impact on their independence and vitality. Cognitive training, physical exercise, enhancement of self-efficacy, social engagement, diet, environmental enrichment, and stress reduction have all been shown to have positive effects on cognition; however, the quality of this evidence varies widely across studies. NIH, in partnership with the McKnight Brain Research Foundation in conjunction with the Foundation for NIH, has initiated a program to convert insights from previous work in cognitive aging into feasible intervention strategies that can be tested in randomized clinical trials. The program's primary goal is to support the initial development and pilot testing of behavioral interventions (individually and in combination) to establish their feasibility, the likely strength of their effects, and immediate and short-term efficacy. These early steps should allow these interventions to move to new clinical trials.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-09-009.html
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIA**)

Viewing Tinnitus in Action: Tinnitus is the perception of sound in the absence of sound (i.e., ringing, roaring, hissing, or clicking sounds in the ears). It is generally associated with age-related or noise-induced hearing loss. In the United States, it affects 12.3 percent of men and nearly 14 percent of women aged 65 and over, and it is the number one cause of service-connected disability for American veterans returning from Iraq and Afghanistan. Very little is known about the neural basis of the disorder. NIH-supported scientists studied a rat model of drug-induced tinnitus combined with brain imaging (microPET and MRI) techniques to identify brain regions in the rat that are affected during tinnitus. Two regions of the brain, consistent with those identified in humans experiencing either noise- or age-induced tinnitus, demonstrated increased activity during drug-induced tinnitus. This study is the first to demonstrate how microPET and MRI techniques can identify brain regions involved in tinnitus. This technique now may be used to study other causes of tinnitus (such as noise) and to evaluate the efficacy of potential therapeutic treatments for tinnitus.

→ Paul AK, et al. *Neuroimage* 2009;44(2):312-8. PMID: 18948211. PMCID: PMC2613016.
→ For more information, see http://www.nidcd.nih.gov/health/hearing/noiseinear.asp
→ (E) (**NIDCD**)

Hearing Loss Is Common in People with Diabetes: In 2008, scientists supported by NIH analyzed data from the 1994-2004 National Health and Nutrition Examination Survey (NHANES), and discovered that hearing loss is about twice as common in adults with diabetes compared to those who do not have the disease. Earlier U.S. studies that examined diabetes and hearing loss found a weaker association or no association, but these studies were based on smaller samples of older adults, and they were not nationally representative (like NHANES). This is the first study of a nationally representative sample of working-age adults, ages 20 to 69 years old, and the data show an association between diabetes and hearing impairment evident as early as ages 30 to 40. Blood flow to the inner ear is essential for normal hearing. Diabetes may lead to hearing loss by damaging the nerves and blood vessels of the inner ear. Autopsy studies of individuals with diabetes have shown evidence of such damage. Additional studies into cochlear blood flow also may shed light on how hearing loss may occur more often in individuals with diabetes.

→ Bainbridge KE, et al. *Ann Intern Med*. 2008;149(1):1-10.
→ For more information, see http://www.nidcd.nih.gov/news/releases/08/06_18_08.htm
→ (E/I) (**NIDCD, NIDDK**)

Neuroprotection Treatment Strategy in Glaucoma: Glaucoma is a group of eye disorders that share a distinct type of optic nerve damage, in which retinal ganglion cells (RGCs) die. Glaucoma is a major public health problem and the leading cause of blindness in African Americans. Elevated intraocular pressure is a common, but not universal, feature of the disease, and pressure-reducing drugs and surgery have been found to delay and reduce severe vision loss from the disease. However, because optic nerve damage is common to all forms of glaucoma, regardless of intraocular pressure, more recent translational research efforts have been targeted toward neuroprotection of the optic nerve. Using gene transfer in a mouse model of glaucoma, NIH investigators overexpressed genes that encode two naturally occurring neuroprotective agents, ciliary-derived neurotrophic factor (CNTF) and brain-derived neurotrophic (BDNF) alone and in combination. Gene transfer with CNTF alone offered the best outcome with a 15 percent improvement in RGC survival compared to control animals. BDNF alone and in combination with CNTF offered modest but not statistically significant protection. Previous studies of CNTF in retinal degenerative diseases found that low doses were neuroprotective while higher doses led to toxicity. Future work will require that dose-response is carefully measured to deliver a safe, optimal therapeutic dose.

→ Pease ME, et al. *Invest Ophthalmol Vis Sci* 2009;50(5):2194-200. PMID: 19060281.
→ For more information, see http://www.iovs.org/cgi/content/full/50/5/2194
→ (E) (**NEI**)

Toward Better Treatment for Muscular Dystrophy: NIH is pursuing multiple pathways to therapeutic development for the muscular dystrophies. NIH funded two new Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers in FY 2008: the Boston Biomedical Research Institute, which seeks to identify biomarkers that can be used in preclinical studies and clinical trials of potential facioscapulohumeral muscular dystrophy (FSHD) therapies, and a center at the University of North Carolina at Chapel Hill, which is developing and testing gene therapies for Duchenne muscular dystrophy (DMD) and other muscle disorders. Collectively, the Wellstone centers program is designed to accelerate the translation of fundamental scientific advances to the clinic (see Chapter 4) and to serve as a national resource for the muscular dystrophy community through core facilities and training programs. NIH funds multiple approaches to therapeutic development through projects outside of the Wellstone program, including a robust portfolio on translational research in muscular dystrophy. Research currently is solicited in this area through two Funding Opportunity Announcements (FOAs) released in 2008: Exploratory/Developmental Projects for Translational Research in Neuromuscular Disease (R21) and the Cooperative Program in Translational Research in Neuromuscular Disease (U01). Previous FOAs on Translational Research in Muscular Dystrophy resulted in a number of funded projects in this area, including projects to develop small molecule drugs and to develop effective gene therapy design and delivery approaches. Progress also is being made toward the GPRA goal to "advance two emerging strategies for treating muscular dystrophy to clinical trial readiness by 2013."

→ For more information, see http://www.wellstonemdcenters.nih.gov/
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NINDS**, NHLBI, NIAMS, NICHD) (COE, GPRA)

Multiple Sclerosis Research: Although the exact cause of multiple sclerosis (MS) is unknown, recent research supported by NIH has begun to identify genetic variations associated with increased risk for developing the disease. In 2007, a genome-wide association study with NIH support reported the first new genetic risk factors for MS to be identified in more than 20 years, and in 2009, meta-analyses and replication studies revealed additional new susceptibility genes. NIH also funds and conducts basic, translational, and clinical research on disease mechanisms, biomarkers, and treatments for MS. For example, NIH supports a randomized, double-blind, placebo-controlled Phase III trial (CombiRx) comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting MS. The trial will determine whether combination therapy offers an improvement over the partial efficacy of either single treatment; it is the only direct comparison of these commonly used medications that is fully blinded and not supported by a commercial entity. NIH's Intramural Neuroimmunology Branch is collaborating with this trial to identify biomarkers associated with different clinical and treatment response profiles (BioMS). Such biomarkers may inform predictions about which treatment will most likely benefit a given patient, making this ancillary study an exciting addition to comparative effectiveness research in MS. Intramural investigators also will collaborate with the Swiss pharmaceutical company Santhera in a Phase I/II clinical trial to test the safety and efficacy of idebenone, which may protect against tissue damage, as a potential treatment for primary progressive MS.

→ De Jager PL, et al. *Nat Genet* 2009;41(7):776-82. PMID: 19525953. PMCID: PMC2757648.
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00211887
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00325988
→ For more information, see http://clinicaltrials.gov/ct2/show/study/NCT00950248
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*
→ (E, I) (**NINDS**)

Advancing Neuroscience Research Through Collaboration

NIH Blueprint for Neuroscience Research: Since its inception in 2004, the NIH Blueprint has been a successful model of trans-NIH collaboration, bringing together 16 NIH ICs and Offices that support neuroscience research. The Blueprint catalyzes research progress by developing tools, resources, and training opportunities that transcend the mission of any single NIH IC and serve the entire neuroscience community. In FY 2008, the Blueprint launched initiatives to develop novel approaches for the study and manipulation of neural circuits as they form during development, a resource for creation and distribution of high-quality monoclonal antibodies for neurodevelopment research, and a gene expression map of the developing rhesus macaque brain. In FY 2009, the Blueprint released a funding announcement supporting research to develop probes, instrumentation, and other tools for understanding, monitoring, and manipulating neural plasticity. In addition, the Blueprint held a workshop focused on translating research on circuit-level plasticity to clinical applications. The Blueprint continues to support training in neuroscience research, clinical assessment tools for neurological and behavioral function, and widely used neuroimaging, neuroinformatics, and genetics and animal model resources. Looking forward, the NIH Blueprint plans to support initiatives addressing Grand Challenges in neuroscience in the areas of pain research, mapping of the human brain, and therapy development for diseases of the nervous system.

→ For more information, see http://www.neuroscienceblueprint.nih.gov
→ (E) (**NIH Blueprint**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

Blueprint Interdisciplinary Research Training: Under the auspices of the NIH Blueprint, interdisciplinary training programs have been established in computational neuroscience, neuroimaging, and translational research in the neurobiology of disease.

- The computational neuroscience programs seek to attract undergraduate and predoctoral students from the physical, mathematical, and engineering sciences to neuroscience research, and to expand the training of neuroscience students in quantitative sciences. Students learn how to develop models of neural systems or processes, test them experimentally, and then use experimental data to refine the models.
- The neuroimaging programs support predoctoral students and summer research intensives and provide comprehensive training in the breadth of imaging techniques and their application to neuroscientific questions. The goal of these programs is to train the next generation of neuroimaging researchers in the limitations, advantages, and underlying principles of currently available neuroimaging modalities.
- The translational research programs support students at multiple stages of their careers. The programs are designed to cross-train students in basic and clinical neuroscience, focusing not on specific diseases but on the biological mechanisms that are shared across diseases.

These Blueprint training programs are successfully seeding the field of neuroscience with highly qualified graduate students, postdoctoral fellows, and faculty.

→ For more information, see http://neuroscienceblueprint.nih.gov/neuroscience_resources/training.htm
→ This example also appears in Chapter 3: Clinical and Translational Research and Chapter 3: Research Training and Career Development
→ (E) (**NIH Blueprint**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

National Database for Autism Research: The National Database for Autism Research (NDAR) is a collaborative biomedical informatics system created by NIH to provide a national resource to support and accelerate research in autism spectrum disorder (ASD). NDAR hosts human genetic, imaging, and phenotypic research data relevant to ASD, making these data available to qualified researchers. NDAR also has the capability to allow investigators to use NDAR for data sharing among select collaborators in ongoing studies. Through its Data Dictionary, NDAR will foster the development of

a shared, common understanding of the complex data landscape that characterizes ASD research. Finally, its architecture facilitates linkage of NDAR with other significant data resources, regardless of their location or ownership and in ways that respect the policies and implementations of those other data resources.

→ For more information, see http://ndar.nih.gov/
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NIMH**, CIT, NICHD, NIDCD, NIEHS, NINDS)

A Clearinghouse for Neuroimaging Informatics Tools and Resources: Many neuroimaging tools and databases are underutilized because they cannot be found easily, are not user-friendly, or are not easily adoptable or adaptable. In an effort to promote the enhancement, adoption, distribution, and evolution of neuroimaging informatics tools and resources, the NIH Blueprint for Neuroscience Research has launched the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC). Examples of included tools are: image segmentation, image registration, image processing pipelines, statistical analysis packages, spatial alignment and normalization algorithms, and data format translators. Resources include: well-characterized test datasets, data formats, and ontologies. Since the first release in October 2007, the clearinghouse website, or NITRC, has become host to 180 tools and resources, with a community of 13,602 unique visitors who downloaded NITRC tools and resources, and 7,000 unique visitors per month, more than 954 of which are registered users (11 percent non-English speaking). The hits to the site have reached 15,635,019/month. Since its inception, more than 50,000 software files have been downloaded. More than 53 percent of the tools on NITRC had not been shared online previously but now are available to the community. In 2009, the NITRC project won the first place of Excellence.gov awards, the largest Federal government award program to recognize the very best in government IT programs, among 61 competitors. Through the initiative, nearly 40 awards have been made to neuroimaging tools and resource developers to enhance the accessibility, interoperability, and adoptability of their existing tools and resources.

→ Ardekani BA, Bachman AH. *Neuroimage* 2009;46(3):677-82. PMID: 19264138. PMCID: PMC2674131.
→ For more information, see http://www.nitrc.org/
→ For more information, see http://neuroscienceblueprint.nih.gov/
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Technology Development*
→ (E) (**NIH Blueprint**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

NINDS Human Genetics Repository: In 2002, NINDS established the Human Genetics Repository to collect, store, characterize, and distribute DNA samples and cell lines and standardized clinical data for the research community. By June 2009, the repository held material from 27,166 subjects, including those with cerebrovascular disease (8,625), epilepsy (1,356), Parkinson's disease (5,700), motor neuron diseases such as amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, (2,631), and Tourette Syndrome (1,185), as well as control samples (6,162). The ethnically diverse collection represents populations from the United States and several other countries. Investigators have submitted or published more than 100 scientific articles based on data from this resource, and technological advances allowing whole genome screening for disease genes also have enhanced its value.

→ For more information, see http://ccr.coriell.org/Sections/Collections/NINDS/?SsId=10
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E, I) (**NINDS**)

Alzheimer's Disease Neuroimaging Initiative (ADNI): ADNI is an innovative public-private partnership for examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease (AD).

ADNI has reached its target enrollment of 800 participants, and supported development of a number of tools and methods now in use in the United States as well as in Japan, the European Union, and Australia. Other expansions include a genome-wide association study of ADNI participants scheduled to provide the most extensive and robust dataset of its kind in the AD field; a study that allows for longitudinal analysis by the collection of additional cerebrospinal fluid from participants over several years; and a study exploring the use of PET and Pittsburgh Compound B (PIB) as a tool for developing biochemical markers. A recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer's and established a method and standard of testing for these biomarkers.

→ For more information, see http://www.loni.ucla.edu/ADNI
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIA**, NIBIB)

Specialized Program of Translational Research in Acute Stroke (SPOTRIAS): The objective of the SPOTRIAS is to serve as an incubator for translational and early-phase clinical research studies. SPOTRIAS sites are located at medical centers where staff have the capacity to evaluate and treat stroke patients very rapidly after symptom onset. NIH supports eight SPOTRIAS sites that have made substantial progress, including impressive increases in tPA use; the establishment of three interlinked repositories for protein and DNA tissue samples, neuroimages, and clinical data; enrollment of more than 951 individuals with acute stroke into treatment protocols; the management of 20 early-phase clinical trials; and the training of 79 research fellows.

→ For more information, see http://www.spotrias.com
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E, I) (**NINDS**)

NIH Establishes Neuro-Ophthalmology Clinical Research Network: The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) Network was established in spring of 2009 to investigate disorders that bridge neurology and ophthalmology and that often are difficult to diagnose and treat. The Network involves more than 200 community and academic practitioners. This consortium will provide a unique opportunity to recruit and study hard-to-find patients to evaluate risks, diagnoses, and treatment options that could not be accomplished without a coordinated effort. The first clinical trial funded under this network will be the Idiopathic Intracranial Hypertension (IIH) Treatment Trial. IIH typically occurs in women of childbearing age. Obesity increases the risk 20-fold. IIH is characterized by an increase in intracranial pressure resulting in blurred vision, double vision, and permanent vision loss. This trial will compare the additional benefit of acetazolamide (a diuretic) added to a low-sodium, weight reduction diet in newly diagnosed patients. Future planned studies include comparing treatments for ocular manifestations in Graves' disease, an autoimmune disorder that causes hyperthyroidism, estimated to affect 2 percent of all women between the ages of 20 and 40. Patients with Graves' can develop protrusion of the eye balls and optic nerve damage. A network of researchers provides valuable expertise and widespread recruitment capabilities for studies of rare disorders.

→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NEI**)

Research on Rare Neurological Disorders: NIH supports research to uncover the causes of and develop treatments for the hundreds of rare disorders that affect the nervous system, while also promoting research on topics such as stem cells, gene therapy, and neuroimaging that will impact multiple rare disorders. NIH reissued a Funding Opportunity Announcement (FOA) for new and renewal applications to continue the Rare Diseases Clinical Research Network (RDCRN), which funds collaborative clinical research consortia focused on rare diseases. NINDS will oversee the

network's Data Management and Coordinating Center, and several of the consortia to be funded through this program focus on neurological disorders, including dystonia, brain vascular malformations, lysosomal storage disorders, and rare diseases of the autonomic nervous system. Through the NINDS translational research program, NIH supports milestone-driven therapy development for rare neurological diseases. Two funded projects, in Batten disease and Niemann-Pick disease, are nearing investigational new drug approval from FDA to conduct clinical trials, and a newly awarded project focuses on gene therapy approaches for the lysosomal storage disorders Tay-Sachs, San Fillipo, and Sandhoff disease. NIH also continues to support and encourage research to understand and treat Ataxia-telangiectasia and dystonia (including rare dystonias) through separate FOAs issued in collaboration with patient organizations.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-272.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-397.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-08-001.html
→ For more information, see http://www.ninds.nih.gov/research/translational/Coop_Tran_Res.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NINDS**, NCI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NICHD, NIDCD, NIDCR, NIDDK, NIEHS, NINR, ODP/ORDR)

National NeuroAIDS Tissue Consortium: The National NeuroAIDS Tissue Consortium (NNTC) is a repository of brain tissue and fluids from highly characterized HIV-positive individuals. Established as a resource for the research community, the NNTC includes information from more than 2,280 participants in its clinical evaluation/tissue donation program, including nearly 750 brains, thousands of plasma and cerebrospinal fluid samples, and additional organs and nerves of interest.

→ For more information, see http://www.hivbrainbanks.org/
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NIMH**, NINDS)

Center for Neuroscience and Regenerative Medicine: The Center for Neuroscience and Regenerative Medicine (CNRM) is a collaborative initiative between NIH and the U.S. Department of Defense (DOD). The center's research mission is to discover methods to better intervene and prevent the long-term consequences resulting from traumatic brain injury (TBI). To increase research capabilities, the United States Congress established the CNRM as a collaborative intramural program and appropriated funds to the DOD for implementation. CNRM will study combat casualties cared for at Walter Reed Army Medical Center (WRAMC) and the National Naval Medical Center (NNMC) using advanced molecular and neuroimaging technology at the NIH CC. The CNRM seeks to serve as the catalyst for collaboration, innovation, and advancement of knowledge of the incidence of TBI and the identification of interdisciplinary approaches to assess TBI and promote recovery. CNRM research programs address the full spectrum of TBI, including the effect of high anxiety and the concurrent development of post-traumatic stress disorder with TBI. In addition, the center will evaluate civilian patients with brain injury following trauma, to understand the relationship between military and civilian brain injury in patients as well as in preclinical models. CNRM research programs focus on (a) diagnostics and imaging, (b) biomarkers, (c) neuroprotection and models, (d) neuroregeneration, (e) neuroplasticity, and (f) rehabilitation and evaluation. The program leverages the strengths of NIH in neurosciences and neuroimaging together with DOD experience in brain trauma, neuroregeneration, and modeling.

→ For more information, see http://www.usuhs.mil/cnrm
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (I) (**CC, NINR**, NIMH, NINDS)

Traumatic Brain Injury Program: Traumatic brain injury (TBI) presents enormous challenges because TBI affects so many people and can compromise virtually any human ability, depending on which parts of the brain are damaged. NIH research ranges from how TBI causes immediate and delayed damage to brain cells, to development of markers of damage, through large clinical trials to test interventions. Multicenter clinical trials now are testing hypothermia (cooling) in children and use of the hormone progesterone to minimize damage in adults. In addition, NIH launched a program to collect data on the use of multidrug combinations to better treat traumatic brain injury. Because the high rate of TBI among military personnel in Afghanistan and Iraq presents a special concern, a Federal Interagency TBI Research group now coordinates among NIH, VA, DOD, and other agencies. Trans-agency workshops have focused on TBI classification (Oct. 2007), combination therapies for TBI (Feb. 2008), opportunities and challenges of blast injury-induced TBI (April 2008), and "Integrated Research on Psychological Health and TBI: Common Data Elements" (March 2009). NIH is working with CDC on how to better track TBI in former military personnel and on evaluating the effectiveness of rehabilitation for TBI. The NINDS intramural research program has worked with the VA and DOD for many years on long-term neuropsychological outcomes of TBI in Vietnam veterans, and now in Iraq veterans. The NIH Intramural Research Program also is partnering now with the Uniformed Health Services University of the Health Sciences Center in the joint Center for Neuroscience and Regenerative Medicine, whose extensive TBI research programs range from molecular studies to understanding TBI mechanisms through rehabilitation and outcomes research.

→ For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Neurological_Effects_of_Blast_Injury_Workshop.htm
→ For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Combination_Therapies_for_Traumatic_Brain_Injury_Workshop.htm
→ For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Classification_of_Traumatic_Brain_Injury_Workshop.htm
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-003.html
→ For more information, see http://www.usuhs.mil/cnrm
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E, E/I) (**NINDS**, CC, NICHD, NIMH, NINR)

Epilepsy Research Benchmarks: In March 2007, more than 400 researchers, physicians, patients, family members, and voluntary organization leaders met on the NIH campus for the "Curing Epilepsy 2007" conference. The meeting followed up on a successful White House-initiated conference held in 2000 that established the first set of Epilepsy Research Benchmarks to guide research directions. The epilepsy research community has made substantial progress since 2000, and attendees at the 2007 conference met to evaluate the original Benchmarks and discuss new directions. Participants voted on topic areas seen as most promising and in need of attention, and NIH solicited public input before the new Benchmarks were released in late 2007. The new Benchmarks for epilepsy research set short- and long-term goals related to preventing epilepsy and its progression; developing new therapeutic strategies and optimizing current approaches toward curing epilepsy; and preventing, limiting, and reversing comorbidities associated with epilepsy and its treatment. One such comorbidity is sudden unexplained or unexpected death in epilepsy (SUDEP). NIH convened a workshop in November 2008 focused on needs for research to understand and prevent SUDEP, and for improving awareness and education about SUDEP for patients, families, and health care providers. Adverse consequences also may be associated with epilepsy treatment, and NIH-supported researchers recently reported that valproate use during pregnancy, as compared to other common antiepileptic drugs, was associated with decreased IQ scores in 3-year old children. Understanding such risks may help patients and their physicians optimize care by allowing more informed choices among available treatment options.

→ Kelley MS, et al. *Epilepsia* 2009;50(3):579-82. PMID: 19317887.
Meador KJ, et al. *N Engl J Med* 2009;360(16):1597-605. PMID: 19369666. PMCID: PMC2737185.
→ For more information, see http://www.ninds.nih.gov/funding/research/epilepsyweb/index.htm
→ (E) (**NINDS**)

Other Notable Examples

High Resolution Anatomical and Functional Imaging of the Human Brain: NINDS and NIMH Intramural Research Programs are partnering to push the frontiers of MRI (magnetic resonance imaging) of the human brain and to make these developments available to researchers. The NINDS Laboratory of Functional and Molecular Imaging has led development of the next generation MRI device that uses a powerful 7T (Tesla) magnet, compared to the usual 1.5T magnetic strength. Overcoming the many technical challenges of imaging at 7T has yielded extraordinarily detailed images, which have contrast and spatial resolution as much as 100 times better than previous methods. These images reveal structures never before seen in the living human brain that may be critical in detecting early stages of disease. The NIMH functional MRI core facility serves more than 30 principal investigators on the NIH Bethesda campus and leads development of functional brain imaging. The facility has played a major role in making 3T MRI widely available for routine use. Together NINDS and NIMH investigators have pioneered imaging methods that increase the detail of structural and functional changes that investigators can detect in the brain, while improving time resolution and shortening duration for brain scans. A two-step strategy to continue this successful program will first translate 7T MRI from its present prototype design to routine use and then develop one of the world's first 11.7T MRI devices for imaging the human brain. Increased MRI resolution will improve diagnosis and monitoring of neurological and psychiatric disorders and open new opportunities for understanding brain function.

→ For more information, see http://intramural.nimh.nih.gov/fmri/fmri_research.html
→ This example also appears in Chapter 3: *Technology Development*
→ (I) (**NINDS**, NIMH)

Lapsing During Sleep Deprivation is Associated with Distributed Changes in Brain Activation: Many serious accidents and medical errors result from lapses of attention that occur when sleep-deprived individuals fail to stay alert. Little is known about the neural correlates of attention lapses, but it appears they may be manifested as delayed or incorrect behavioral responses to certain stimuli. These attention lapses occur even after a normal night's sleep, becoming longer in duration and more frequent after sleep deprivation, suggesting that an underlying cause may be due to transient disruptions of cognitive control processes that rely on activation of the frontal lobes in the brain. To identify changes in task-associated brain activation associated with attention lapses, a group of NIH-supported researchers collected functional magnetic resonance images from healthy adults during a visual, selective attention task following sleep deprivation. The research findings reveal alterations in brain activity that occur as a result of sleep deprivation and the consequences of these changes to daily behaviors, including reduced abilities to maintain visual attention and process visual information. Understanding how the sleep-deprived brain impacts our ability to perceive and process information, as well as attend to everyday tasks, may lead to new discoveries that will address the underlying causes and symptoms of sleep deprivation.

→ Chee MW, et al. *J Neurosci* 2008;28(21):5519-28. PMID: 18495886.
→ For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18495886
→ (E) (**NINR**)

A Light Shines on Brain Circuits: NIH-funded researchers have devised an innovative method for modulating distinct brain circuits in the cortex. Calling their method “optogenetics,” the researchers genetically engineered mouse neurons to be sensitive to fluorescent light in such a way that different colors of fluorescent light served as an on/off switch for the neurons. The researchers then were able to expose these mouse brain cells to specific kinds of fluorescent light to selectively block or enhance brain cell activity. They found that when they blocked the activity of a class of neurons, they eliminated a specific frequency range of circuit activity, whereas when they heightened activity of these cells, synchronized rhythm emerged. The combination of neuronal and synchronized rhythmic activities enhanced overall circuit function by boosting signal and reducing noise, making the messages transmitted between neurons loud and clear. The

optogenetic approach presents a new and highly selective way of analyzing brain function, enabling researchers to determine the roles of different factors affecting brain performance and pathology.

→ Sohal VS, et al. *Nature* 2009;459(7247):698-702. PMID: 19396159.
Cardin JA, et al. *Nature* 2009;459(7247):663-7. PMID: 19396156.
→ (E) (**NIMH**)

Clinical Research and Trials in Neurological Disease: NINDS funds more than 1,000 extramural clinical research studies. Clinical researchers are studying, for example, disease mechanisms, risk factors that contribute to health disparities, brain imaging, and genes that predispose to disease as well as conducting multisite clinical trials that test the safety and efficacy of new prevention strategies and treatments or compare existing interventions. In the past year, for example, an NICHD/NINDS clinical trial reported that a drug commonly used to delay labor can prevent cerebral palsy in some circumstances, and a Veterans Administration/NINDS trial demonstrated that deep brain stimulation, a surgical intervention, is more effective than drug treatment at improving movement and quality of life for many people who have Parkinson's disease, but carries some risks. Among trials now underway, researchers are testing interventions to protect the brain following traumatic brain injury, to prevent stroke, to slow the progression of neurodegenerative diseases, and to treat multiple sclerosis. An independent study contracted by NINDS found that NINDS clinical trials which cost $335 million over 10 years provided benefits that exceeded $15 billion and added 470,000 healthy years of life to people in the United States. With guidance from an expert strategic planning panel, NINDS is continuing to improve the efficiency and payoff of the clinical trials program.

→ Johnston SC, et al. *Lancet* 2006;367:1319-27. PMID: 16631910.
Weaver FM, et al. *JAMA* 2009;301(1):63-73. PMID: 19126811.
Rouse DJ, et al. *N Engl J Med* 2008;359(9):895-905. PMID: 18753646.
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NINDS**, NICHD)

Translational Research for Neurological Disorders: The Anticonvulsant Screening Program has catalyzed the development of six epilepsy drugs now on the market; the Neural Prosthesis Program has pioneered devices to restore lost nervous system functions; the Intramural Program has developed the first enzyme therapy for inherited disorders; and investigator-initiated research programs have led to development of FDA-approved drugs by industry. In 2003, NIH launched a program designed to expedite preclinical therapy development across all neurological disorders. The Cooperative Program in Translational Research supports academic and small business investigator-initiated projects in single laboratories or consortia, using milestone-driven funding and peer review tailored to the requirements of therapy development. Projects are developing drug, stem cell, or gene therapies for amyotrophic lateral sclerosis (ALS), Batten disease, epilepsy, Huntington's disease, muscular dystrophies, Parkinson's disease, tuberous sclerosis, and stroke, among other disorders. NIH also has developed several focused translational research initiatives over the last decade. The Spinal Muscular Atrophy (SMA) Project, for example, is an innovative pilot program to develop a treatment for SMA using a "virtual pharma" strategy that engages resources to carry out a drug development plan via contracts and collaboration. The project has two patents on compounds that show promise and is evaluating the safety of the most promising drug candidates, with the goal to begin human clinical trials as soon as possible. Translational research is a "signature project" for NINDS investment of American Recovery and Reinvestment Act funds.

→ For more information, see http://www.ninds.nih.gov/funding/research/translational/index.htm.
→ For more information, see http://www.ninds.nih.gov/research/asp/index.htm
→ For more information, see http://www.ninds.nih.gov/research/translational/index.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NINDS**) (ARRA)

Brain Tumor Research: NIH funds studies aimed at understanding the development and treatment of central nervous system and peripheral nervous system tumors, including medulloblastoma, neuroblastoma, and glioblastoma, as well as research on several inherited neurological tumor syndromes, including neurofibromatosis and tuberous sclerosis complex. In the past few years NIH has released a number of funding opportunity announcements (FOAs) related to brain tumor research. A FOA on understanding and preventing brain tumor dispersal has been particularly effective in stimulating this area of research and has led to exciting advances. NIH also funds clinical studies investigating therapy delivery to the brain and evaluating the safety and tolerability of various therapies, including immunological therapies, vaccine therapy, monoclonal antibodies, and combination therapies. The Surgical and Molecular Neuro-Oncology Unit within the NIH Division of Intramural Research investigates basic mechanisms of brain tumor development and chemotherapy resistance to find new therapeutic strategies, particularly for malignant gliomas. NINDS and NCI co-lead the Trans-NIH Brain Tumor Working Group.

→ For more information, see http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-08-048.html
→ This example also appears in Chapter 2: *Cancer*
→ (E, I) (**NINDS**, NCI)

Peripheral Neuropathies: NIH funds studies focused on understanding the genetic basis and molecular and cellular mechanisms of many peripheral neuropathies, including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, inherited neuropathies such as Charcot-Marie-Tooth, inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy, and rare forms of peripheral neuropathy. Other notable projects include a natural history study of diabetic neuropathy, projects to improve the efficiency and effectiveness of diagnosis for various peripheral neuropathies, and a Phase III clinical trial to treat Familial Amyloidotic Polyneuropathy. In August 2008, a pair of program announcements was released to promote translational research in neuromuscular disease. Diseases included in these program announcements are those that affect the motor unit—the motoneuron, its process (axon), and the skeletal muscle fiber that is innervated by the neuron—such as peripheral neuropathy, amyotrophic lateral sclerosis, and muscular dystrophy. This unique structure-function framework provides a coordinated approach for therapeutic development in a subset of neurological diseases that share many common features, including the peripheral neuropathies.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NINDS**, NIDDK)

From Genes to Therapy in Neurogenetic Disorders: Neurofibromatosis (NF) and tuberous sclerosis complex (TSC) are neurogenetic disorders that cause tumors on nerves, in the brain, and on other organs. Although the tumors are benign, consequences of their size and location can be serious. Clinical manifestations can include seizures, autism, and cognitive disability. NIH support led to identification of the genes underlying these disorders, and recently has enabled investigators to uncover disease mechanisms that point to strategies for therapeutic development. One NF study revealed that an NF1 gene mutation in bone marrow cells (which infiltrate peripheral nerves prior to NF tumor development) is necessary for tumor growth. Activation of c-kit, a molecule implicated in some cancers and targeted by the cancer drug Gleevec, enables release of the cells from bone marrow to stimulate neurofibroma growth. In this study, Gleevec treatment prevented formation and reduced neurofibroma size and activity. If clinical trials prove successful, Gleevec could become the first approved NF treatment. In TSC, genetic mutations cause deregulation of an anti-tumor molecule, mTOR, which is a known target of rapamycin (a drug currently used to treat organ transplant rejection). In previous studies, rapamycin reduced the size of brain and kidney tumors in TSC patients. Recent NIH-supported research in mice revealed that rapamycin, via the mTOR pathway, inhibited TSC-induced brain enlargement and mortality, prevented seizures, and improved cognitive ability in mice, results which have led to clinical trials now in Phase III. Rapamycin also alleviated

seizures in a rat model of epilepsy, which may shed light on TSC-associated neurological diseases, including autism and epilepsy.

→ Ehninger D, et al. *Nat Med* 2008;14(8):843-8. PMID: 18568033. PMCID: PMC2664098.
Meikle L, et al. *J Neurosci* 2008;28(21):5422-32. PMID: 18495876. PMCID: PMC2633923.
Yang FC, et al. *Cell* 2008;135(3):437-48. PMID: 18984156. PMCID: PMC2788814.
Zeng LH, et al. *J Neurosci* 2009;29(21):6964-72. PMID: 19474323. PMCID: PMC2727061.
Zeng LH, et al. *Ann Neurol* 2008;63(4): 444-53. PMID: 18389497.
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NINDS**, NCI, NICHD, NIMH)

Know Stroke Efforts and New Stroke Slogan: In 2004, NIH entered a partnership with CDC to launch a grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders who work as "Stroke Champions" to educate their communities about the signs and symptoms of stroke and the need for immediate action. The program focuses on reaching African Americans, Hispanics, and seniors in communities that have the health care systems in place to treat stroke. To date, the program has been implemented in 12 cities, educating 184 Stroke Champions who have conducted more than 600 community events. The program was expanded this year to Charleston, South Carolina, and, as a follow-up to that program, materials will be developed for coastal communities with unique dialects. NIH also recently expanded its public education programs by collaborating with the Brain Attack Coalition (BAC) to develop a new action-oriented message that all member organizations could use with their current stroke awareness efforts. The BAC is a group of organizations committed to stroke prevention and treatment chaired by NINDS. The new slogan—"Stroke strikes fast. You should too. Call 9-1-1."—was launched in May 2009 during Stroke Awareness Month.

→ For more information, see http://stroke.nih.gov/about/
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (O) (**NINDS**)

Reducing Disparities in Stroke: NIH actively is engaged in a number of research projects designed to identify risk factors for stroke in minority populations and enhance prevention and treatment in these groups. The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study is an observational study to explore the role of race and geographic differences on stroke risk factor prevalence and stroke incidence and mortality. Recruitment of the main REGARDS cohort was completed at the end of 2007 with 30,229 participants (41 percent African American and 59 percent white, 55 percent female and 45 percent male), and includes participants from 1,833 of the 3,111 counties (59 percent) in the 48 contiguous United States. The group already has published a number of important findings that partially explain why African Americans and residents of the southeastern "Stroke Belt"" have higher risk of dying from stroke, and also findings documenting the consequences of not reporting stroke symptoms, including poor health outcomes and death. NIH also has established an acute stroke research and care center at the Washington Hospital Center (WHC), a community hospital in Washington, DC, where more than 75 percent of stroke patients are African American or Hispanic. The center will collect data to aid in stroke prevention programs and will run two clinical trials, one on secondary stroke prevention and another on increasing tPA use among minorities. The program directly addresses GPRA goal: *By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities*.

→ Howard G, et al. *Prev Med* 2009;49(2-3):129-32. PMID: 19285103. PMCID: PMC2778033.
Cushman M, et al. *Ann Neurol* 2008;64(5):507-13. PMID: 19067365. PMCID: PMC2802965.
Howard G, et al. *Stroke* 2007;38(9):2446-52. PMID: 17673720.
Wadley, G, et al. *Stroke* 2007;38:1143-1147. PMID: 17322077.
→ For more information, see http://www.regardsstudy.org/index.htm
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E, I) (**NINDS**) (GPRA)

NIH Countermeasures Against Chemical Threats (CounterACT) Research Program: The CounterACT Research Network, as reflected in an NIH GPRA goal, develops medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The Network, which has collaborated with the U.S. Department of Defense (DOD) from its inception in 2006, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. One promising countermeasure, midazolam, which DOD researchers identified as a potential countermeasure against chemical agent-induced seizures, has entered clinical trials through the NIH Neurological Emergency Clinical Trials Network, and NIH is collaborating with DOD to complete animal studies necessary for its FDA approval as a nerve agent treatment. The New Drug Application is expected early FY 2010, with approval anticipated by the end of the year. The network also has developed six other lead compounds as therapeutics for cyanide, nerve agent, chlorine, and sulfur mustard, and has participated in pre-Investigational New Drug application meetings with FDA related to these efforts. One of the diagnostic devices developed by the program is being used in an NIH clinical trial. Three chemical agent therapeutics developed by the program also show promise as therapies for radiation exposures, and the program is collaborating with the NIH Medical Countermeasures Against Radiological and Nuclear Threats program.

- → For more information, see http://www.ninds.nih.gov/research/counterterrorism/counterACT_home.htm
- → For more information, see http://clinicaltrials.gov/ct2/show/NCT00809146
- → For more information, see http://nett.umich.edu/nett/welcome
- → This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
- → (E) (**NINDS**, NEI, NIAID, NIAMS, NICHD, NIEHS, NIGMS) (GPRA)

Acupuncture Shows Possible Effect for Tension Headaches: Millions of Americans suffer from chronic headaches. Tension headaches—characterized by pain/discomfort from tense/constricted muscles in the head, neck, or scalp—are a common form of headache. In most patients, tension headaches occur infrequently and can be treated with over-the-counter pain medicine. However, some people experience the headaches several days per month, even daily, and may benefit from other treatments. A review published by the Cochrane Collaboration looked at literature on acupuncture for tension headaches and analyzed findings from 11 randomized trials with 2,317 participants that compared acupuncture with a control or simulated acupuncture. The systematic review selected randomized trials with a post-randomization observation period of at least 8 weeks that compared clinical effects of an acupuncture intervention with a control (treatment of acute headaches only or routine care), a simulated acupuncture intervention, or another intervention in patients with episodic or chronic tension headache. The results of the literature review found that of the 11 studies: Two showed that patients who received acupuncture in addition to standard care had fewer headaches. Five found slightly better effects in patients who received true acupuncture compared with simulated acupuncture. Three of the four trials that compared acupuncture with physiotherapy, massage, or relaxation had methodological limitations. Their findings were difficult to interpret, but acupuncture appeared to have slightly better results than other therapies. The researchers concluded that acupuncture could be an option for patients suffering from frequent tension headaches.

- → Linde K, et al. *Cochrane Database Syst Rev* 2009;(1):CD007587. PMID: 19160338.
- → For more information, see http://nccam.nih.gov/research/results/spotlight/031709.htm
- → (E) (**NCCAM**)

Comorbidity: Addiction and Other Mental Disorders: Drug addiction frequently is accompanied by other psychiatric diseases, which can complicate its diagnosis and treatment. Thus, NIH supports research on the multiple facets of psychiatric comorbidity across multiple health sectors. This approach explores whether drug use leads to mental illness or the reverse, what causes their frequent co-occurrence (e.g., shared genetic and environmental vulnerabilities or similarities in brain circuits and chemical messengers), and how to treat both comprehensively. Specific activities include epidemiological research on mental health/drug abuse comorbidity, such as secondary analyses of data from the National

Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study and the National Comorbidity Survey to better understand the prevalence and variety of comorbidities, and clinical trials to help assess the actions of combined or dually effective behavioral and medication treatments (e.g., in adolescent and adult patients with attention deficit/hyperactivity disorder [ADHD] and substance abuse problems). It also includes a push for research to investigate drug abuse and mental health screening for all those entering the criminal justice system, a notable gap, particularly for adolescents. Another identified gap calls for research using preclinical models of comorbidity to explore the neurological bases of comorbid drug abuse and other mental illness (e.g., overlapping circuitry). Joint requests for applications issued by multiple ICs have elicited studies examining everything from the role of depression and anxiety in the tobacco epidemic to the neural bases of ADHD in fetal drug or alcohol exposure to improving care for co-occurring disorders in rural areas via new technologies. (Note: NESARC and the National Comorbidity Survey are nationally representative surveys in the United States that assess the prevalences and correlates of DSM-III-R disorders, including substance use and mental health disorders.)

→ For more information, see http://www.drugabuse.gov/CTN/protocol/0028.html
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0029.html
→ For more information, see http://www.nida.nih.gov/ResearchReports/comorbidity
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**, NIAAA, NIMH)

NIH Strategic Plans Pertaining to Neuroscience and Disorders of the Nervous System

National Institute of Neurological Disorders and Stroke (NINDS)

- *Neuroscience in the New Millennium*
- *Benchmarks for Epilepsy Research*
- *Report of the Stroke Progress Review Group*
- *The 2006 Parkinson's Disease Research Plan*

National Eye Institute (NEI)

- *National Eye Institute Strategic Planning*
- *National Plan for Eye and Vision Research* (2004)
- *Progress in Eye and Vision Research 1999-2006*
- *Ocular Epidemiology Strategic Planning Panel Report—Epidemiological Research: From Populations Through Interventions to Translation* (2007)
- *Age-Related Macular Degeneration Phenotype Consensus Meeting Report*
- *Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration Workshop Report*
- *Report of the Advances in Optical Imaging Symposium*

National Institute on Aging (NIA)

- *Living Long and Well in the 21st Century: Strategic Directions for Research on Aging*

National Institute on Deafness and Other Communication Disorders (NIDCD)

- *FY 2006-FY 2008 NIDCD Strategic Plan*
- *FY 2009-FY 2011 NIDCD Strategic Plan*

National Institute of Mental Health (NIMH)

- *The National Institute of Mental Health Strategic Plan*

National Institute on Drug Abuse (NIDA)

- *NIDA Five-Year Strategic Plan 2009*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- *National Institute on Alcohol Abuse and Alcoholism Five Year Strategic Plan FY 08-13*

  Recommendations of the NIAAA Extramural Advisory Board (EAB)

  - *Mechanisms of Alcohol Addiction*
  - *Medications Development*

National Center for Complementary and Alternative Medicine (NCCAM)

- *Expanding Horizons of Health Care: Strategic Plan 2005-2009*

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

- *Neuroscience Research Support at NICHD*

  Branch Reports to Council with Future Research Directions:

  - *Child Development and Behavior Branch (CDBB), NICHD, Report to the NACHHD Council, January 2009*
  - *National Center for Medical Rehabilitation Research (NCMRR), NICHD, Report to the NACHHD Council, January 2006*
  - *Developmental Biology, Genetics, and Teratology Branch, Report to the NACHHD Council, September 2006*
  - *Mental Retardation and Developmental Disabilities Branch, NICHD, Report to the NACHHD Council, June 2005*

Fogarty International Center (FIC)

- *Pathways to Global Health Research: Strategic Plan 2008-2012*

Office of AIDS Research (OAR)

- *FY 2008 Trans-NIH Plan for HIV-Related Research*
- *FY 2009 Trans-NIH Plan for HIV-Related Research*
- *FY 2010 Trans-NIH Plan for HIV-Related Research*

Other Trans-NIH Plans

- *Research Plan for Tuberous Sclerosis*
  (NCI, NHLBI, NIAMS, NICHD, NIDDK, NIMH, **NINDS, ORD**)
- *Muscular Dystrophy Research and Education Plan for the NIH*
  (**NINDS, NIAMS, NICHD** [co-leads])

- *Action Plan for the Muscular Dystrophies*
  (**NINDS, NIAMS, NICHD** [co-leads])
- *Report of the Brain Tumor Progress Review Group*
  (**NCI**, NINDS)
- *Research Plan for Ataxia-Telangiectasia*
  (NCI, NCRR, NEI, NHLBI, NHGRI, NIA, NIAID, NICHD, NIEHS, NIGMS, **NINDS**, ORD)
- *NIH Research Plan on Down Syndrome*
  (**NICHD**, NCI, NHLBI, NIA, NIAID, NIDA, NIDCD, NIDCR, NIMH, NINDS)
- *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*
  (CC, CSR, NCCAM, NCI, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, **NIDDK**, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)
- *NIH Research Plan on Fragile X Syndrome and Associated Disorders*
  (**NICHD**, NIMH, NINDS, NIA, NIDDK, NIGMS, NCI, NIDCD)

Interagency Plans

- *2009 Strategic Plan for Autism Spectrum Disorder Research*
  (**NIH** [**NIMH**, NICHD, NIEHS, NIDCD, NINDS])**,** ACF, CMS, CDC, HRSA, SAMHSA, HHS Office on Disability, U.S. Department of Education)

[11] Institutes and Centers participating in the NIH Blueprint for Neuroscience Research: NEI, NIA, NIAAA, NIBIB, NCCAM, NICHD, NCRR, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, and OBSSR.
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Infectious Diseases and Biodefense

In April 2009, a new strain of the influenza virus emerged in Mexico and quickly spread around the globe. Because of its experience responding rapidly to emerging disease threats, NIH was poised to quickly mount a major research effort to learn about this new virus strain and to develop approaches to reduce its impact on public health. The virus now is known as 2009 H1N1 influenza A. Building on a strong foundation of basic research on influenza viruses, NIH was engaged fully in the government-wide effort to understand the biology of the 2009 H1N1 influenza virus and its interaction with humans, and to rapidly develop effective vaccines and therapies. NIH used its longstanding vaccine clinical trials infrastructure to quickly evaluate pilot lots of vaccine candidates to determine their safety and ability to induce protective immune responses, and to ascertain the appropriate dose and number of doses needed for immunization. NIH-supported trials included studies of specific populations, such as pregnant women, children, HIV-infected individuals, and people with asthma, along with trials of healthy adults and elderly. This information was crucial in informing the establishment of public health guidelines for H1N1 vaccines. By conducting essential research, and by establishing effective partnerships with international agencies, other Federal agencies, and private industry, NIH was instrumental in the effort to prepare a 2009 H1N1 influenza vaccine in time for the fall 2009 Northern Hemisphere flu season.

Introduction

The goals of NIH-supported research on infectious diseases and biodefense rest on two core components. NIH builds and maintains a base of fundamental knowledge about infectious and immune-related diseases and uses that knowledge to develop new and improved diagnostics, therapeutics, and preventive measures, including vaccines. At the same time, NIH continues to develop a flexible domestic and international infrastructure that allows it to respond to newly emerging and re-emerging threats wherever they occur, thereby protecting public health in the United States and abroad.

Infectious Diseases

Infectious diseases are caused by microbial pathogens—bacteria, viruses, fungi, protozoa, and helminths (worms)—that invade the body and multiply, causing physiological damage and illness. Pathogens cause a range of diseases from minor to life-threatening and can be transmitted in many ways. Influenza and tuberculosis (TB) can be transmitted from person to person via airborne inhalation; HIV, which causes AIDS, is transmitted through exposure to blood or other body fluids; and malaria is caused by a microscopic parasite that is transmitted by an insect "vector," in this case a mosquito. Transmissible infectious diseases can devastate large human populations rapidly and easily cross international borders.

Biodefense and Emerging and Re-emerging Infectious Diseases

Public health threats that could cause large-scale disruption and devastation include the deliberate or accidental release of pathogenic agents such as anthrax or smallpox, biological toxins, chemical weapons such as nerve gas, or radioactive substances. Threats to public health change continually as new pathogens emerge, and as familiar microbes reemerge with new properties or in unusual settings. The NIH biodefense strategy integrates basic, applied, and clinical research knowledge and capabilities into a flexible and adaptable approach designed to create interventions that target single as well as multiple pathogens. Examples of recent emerging and re-emerging public health threats include naturally occurring infectious diseases such as 2009 H1N1 and H5N1 influenza, Ebola hemorrhagic fever, and severe acute respiratory syndrome (SARS). The overall goal of research on biodefense and emerging and re-emerging infectious diseases is to develop the knowledge and tools to respond quickly and effectively as public health threats emerge, whether they occur naturally, accidentally, or deliberately.

Although NIAID has primary responsibility for infectious diseases and biodefense research, many other NIH ICs play critical roles, including FIC, NICHD, NIEHS, NINDS, and OAR. All of the NIH ICs support AIDS-related research

activities, consistent with their individual missions. The ICs that conduct most of the research on AIDS and its associated co-infections, malignancies, cardiovascular and metabolic complications, and behavioral and social science issues are NIAID, NIDA, NCI, NIMH, NCRR, NICHD, and NHLBI. All NIH AIDS research is coordinated by OAR.

In addition, the NIH Office of Science Policy manages and supports the National Science Advisory Board for Biosecurity (NSABB). Taking into consideration national security concerns and the needs of the research community, the NSABB provides advice on strategies for the efficient and effective oversight of dual-use biological research—research that has a legitimate scientific purpose but if misused could pose a threat to public health or national security (also see the section on *Ensuring Responsible Research* in Chapter 1).

NIH-wide research on infectious diseases and biodefense includes basic research to understand fundamental mechanisms by which microorganisms cause disease, the host response to pathogens, and mechanisms by which insects and other vectors transmit infectious diseases. Translational research builds on basic research findings with the aim of developing new and improved diagnostics, therapeutics, vaccines, and other preventive measures. NIH conducts and supports clinical research to assess the efficacy and safety of candidate drugs, vaccines, and other products. As NIH pursues these goals, an overarching priority is to reduce health disparities and improve health for all people.

Infectious diseases and biodefense inherently are global concerns. NIH engages in international partnerships to improve means for detecting and controlling the spread of infectious diseases and supports international programs to foster research and research capacity in developing countries. Within the United States, NIH seeks strategic partnerships with other governmental and nongovernmental organizations.

Infectious diseases and biodefense inherently are global concerns. NIH engages in international partnerships to improve means for detecting and controlling the spread of infectious diseases and supports international programs to foster research and research capacity in developing countries.

NIH supports research on HIV/AIDS, TB, malaria, emerging and re-emerging infectious diseases (such as hemorrhagic fevers caused by Ebola and other viruses, West Nile virus, SARS, Lyme disease, prion diseases, and H5N1 [a virus that causes avian influenza]), sexually transmitted infections, and influenza and other respiratory infections. In addition, NIH funds research on many less familiar but still important diseases that exact an enormous global toll.[28]

NIH research on biodefense and emerging and re-emerging infectious diseases necessarily is intertwined and includes the development of infrastructure and capacity-building, that is, facilities and human resources needed to conduct research on dangerous pathogens safely and effectively; basic research on microbes and host immune defenses; the targeted development of medical countermeasures, including vaccines, therapeutics, and diagnostics; and training for emergency and skilled workers that would be needed in the event of a biological, chemical, or radiological weapons attack or other public health emergency.

Burden of Illness and Related Health Statistics

Infectious diseases cause approximately 26 percent of all deaths worldwide. Each year, more than 11 million people die from infectious diseases; the vast majority of deaths occur in low- and middle-income countries. The top infectious disease killers in those countries for people ages 15 to 59 are HIV/AIDS, TB, and lower respiratory infections.[29] Worldwide, HIV causes nearly 2.0 million total deaths each year,[30] TB kills 1.6 million each year,[31] and lower respiratory infections in 2005 caused an estimated 3.7 million deaths.[32] Malaria is a serious problem, especially in Africa, where one in every five childhood deaths is due to the effects of the disease.[33] The infectious diseases that today cause the greatest number of human deaths worldwide are (in order) lower respiratory infections, HIV/AIDS, diarrheal diseases, malaria, and TB.[34]

Each year infectious diseases kill approximately 6.5 million children, most of whom live in developing countries. For children younger than age 14, infectious diseases account for 7 of the top 10 causes of death. In this age group, the leading infectious diseases are lower respiratory infections, diarrheal diseases, and malaria. Among children younger than age 5, infectious diseases cause about two-thirds of all deaths.[35]

Each year infectious diseases kill approximately 6.5 million children, most of whom live in developing countries. For children younger than age 14, infectious diseases account for 7 of the top 10 causes of death.

The burden of infectious diseases is not evenly shared, even among developing nations. People who live in sub-Saharan Africa are most affected, particularly by HIV/AIDS, which accounts for one in five deaths in that region. Africa and the most populous countries of Asia harbor the largest number of TB cases. Together, Bangladesh, China, India, Indonesia, and Pakistan account for half of new TB cases each year.[36]

In the United States, infectious diseases add significantly to the overall burden of illness. Together, influenza and pneumonia account for more than 56,000 deaths annually.[37] More than a million cases of sexually transmitted diseases occur each year, including 56,400 new HIV infections, and more than 37,000 new cases of AIDS were reported in 2007.[38]

Also, many infectious diseases increasingly are difficult to treat because pathogens are developing resistance to antimicrobial drugs. For example, in recent years there have been dramatic increases in antiretroviral drug resistance in HIV, chloroquine resistance in malaria, the emergence of multidrug-resistant TB (MDR TB) and extensively drug-resistant TB (XDR TB), and methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

NIH Funding for Infectious Diseases and Biodefense Research

Actual NIH funding support levels for infectious diseases research were $3,575 million in FY 2008, and $3,627 million and $526 million in FY 2009, respectively, for non-ARRA (regular appropriations) and ARRA (Recovery Act appropriations). Actual funding levels for biodefense research were $1,736 million in FY 2008, and $1,746 million and $213 million in FY 2009, respectively, for non-ARRA and ARRA. There is substantial overlap between the funding figures for infectious diseases research and biodefense research. Click on the funding levels, which are live links, to produce detailed project listings. These lists are derived from the NIH Research, Condition, and Disease Categorization (RCDC) system. In addition, the table at the end of this chapter indicates some of the research areas involved in these investments (see *Estimates of Funding for Various Research, Condition, and Disease Categories*).

Summary of NIH Activities

NIH programs on infectious diseases and biodefense encompass a broad portfolio of basic, translational, preclinical, and clinical research. These activities include developing critical infrastructure and research resources, and providing training to develop scientific expertise in the United States and abroad. These activities allow NIH to mount an effective research response to public health threats wherever they occur.

Basic Research

NIH basic research on infectious diseases and biodefense seeks to illuminate the fundamental biology and interactions of pathogens and hosts. The knowledge gained provides the foundation for improvements in prevention, diagnosis, and treatment of infectious diseases and contributes to our country's preparedness against the threat of bioterrorism as well as naturally occurring disease outbreaks. Basic research spans topics from genes to global climate change to the use of technologies such as bioinformatics, proteomics, and systems biology to evaluate pathogens.

In its intramural and extramural programs, NIH conducts and supports genome sequencing of pathogens and hosts that helps reveal how microbes evolve, infect host cells, cause disease, develop drug resistance, and spread. As patterns of disease transmission reflect the impact of environmental changes, NIH-supported researchers seek to identify the mechanisms by which insects and other vectors transmit infectious disease.[39] On a global level, researchers pursue interdisciplinary research to decipher the underlying ecological and biological mechanisms that govern relationships between human-induced environmental changes and the emergence and transmission of infectious diseases[40] including influenza, malaria, and dengue.

An important facet of NIH-supported research is the effort to expand understanding of human immune responses. The Adjuvant Development Program, launched in 2008, builds on the successful Innate Immune Receptors and Adjuvant Discovery Program. The goal is to identify existing adjuvants—substances added to stimulate or boost an immune response—that could be licensed for human use in vaccines against infectious agents such as influenza, TB, and West Nile virus. In 2008, researchers found that the adjuvant alum activates the innate immune system by stimulating clusters of proteins called inflammasomes, found inside certain cells.[41] This finding enhances understanding of adjuvant function and may facilitate the design of new adjuvants.

The Adjuvant Development Program, launched in 2008, aims to identify substances that can be added to vaccines to boost immune responses to infectious agents such as influenza, TB, and West Nile virus.

NIH also is intensifying its focus on primary immune deficiency diseases (PIDD), which dramatically increase susceptibility to infections. In 2007, NIH opened the Primary Immune Deficiency (PID) Clinic on the NIH campus. PID Clinic scientists reported that a mutation in the gene *DOCK8* might underlie a newly identified category of PIDD, tentatively called DOCK8 immunodeficiency syndrome.

Other basic research seeks to understand how complex, multichain sugar molecules called oligosaccharides might act as antimicrobial agents that help prevent bacterial and viral infections of the digestive tract.[42] These oligosaccharides are present in human milk, but are non-nutritive, raising the question of why they persist in evolution. The research could lead to novel approaches for synthesizing antimicrobial oligosaccharides to treat people who have been exposed to gastrointestinal pathogens.

Basic research initiatives launched in 2009 focus on investigating the linkages between malnutrition and intestinal infections and their effects on children in the developing world;[43] supporting a program to build on recent advances in immune profiling to measure the diversity of human immune responses to infection or vaccination; discovering how the lung microbiome—the mix of microorganisms that inhabit the respiratory tract—might increase the likelihood of severe respiratory problems in people infected with HIV;[44] and advancing understanding of the risks, development, progression, diagnosis, and treatment of malignancies—including hepatocellular carcinoma—in individuals with underlying HIV infection or AIDS.

Research on the causes of antimicrobial resistance (such as how bacteria develop and share resistance genes) explores how disease-causing bacteria such as MRSA and vancomycin-resistant *S. aureus* (VRSA) develop resistance to previously effective antibiotics.[45] NIH is conducting clinical tests to evaluate the efficacy of off-patent antimicrobial agents as possible interventions for the effective treatment of hospital-acquired MRSA infection.

Research on the causes of antimicrobial resistance (such as how bacteria develop and share resistance genes) explores how disease-causing bacteria such as methicillin-resistant S. aureus (MRSA) and vancomycin-resistant S. aureus (VRSA) develop resistance to previously effective antibiotics.

NIH basic and translational research includes studies using animal models to determine how bone marrow stromal cells, which help modulate immune responses, might be used to treat sepsis, the widespread activation of inflammation and blood clotting pathways that can accompany a severe infection and lead to multiple organ failure, septic shock, and death.[46]

Major Infectious Diseases

NIH conducts research on hundreds of infectious diseases, with special emphasis on those that claim large numbers of lives each year. Research includes studies of major infectious diseases such as TB, malaria, and HIV/AIDS, as well as studies to ensure the health of special populations—individuals whose immune systems are compromised, the elderly, adolescents, young children, and infants. NIH also explores how human behaviors as well as social, cultural, economic, and geographic factors affect disease transmission. The ultimate goal is to translate knowledge gained through basic research into interventions that improve public health in the United States and other countries.

Tuberculosis

TB, an ancient disease, remains one of the major causes of disability and death worldwide. It also is a prototypical example of a re-emerging disease, due to the HIV/AIDS co-epidemic and an increase in the prevalence of drug-resistant forms of the bacillus *Mycobacterium tuberculosis* (*Mtb*) that are much more difficult to treat. Persons co-infected with HIV often have weakened immune systems and are much more likely to develop active TB disease after infection with *Mtb*. HIV co-infection increases the risk of developing active TB by a factor of 20 or more.[47]

NIH continuously is expanding its TB research program using state-of-the-art technologies to develop new tools for rapid, early diagnosis; new vaccines to prevent TB; and improved therapies for all forms of the disease, including drugs for MDR TB and XDR TB. Researchers are working to understand the basic biology and immunology of TB; improve clinical management of MDR TB and XDR TB in people with and without HIV infection, including children; and prevent TB by various means, including vaccines.[48]

Some of this research already has borne fruit. Investigators found that two FDA-approved drugs, meropenem and clavulanate—used to treat other bacterial diseases—work in tandem to kill *Mtb* in laboratory models.[49] A clinical trial is being developed to test the combination in people who have drug-resistant TB.[50] Also, NIH-supported clinical trials showed that mortality among persons with TB who are co-infected with HIV drops markedly when they receive antiretroviral (ARV) therapy and TB therapy concurrently.

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To address problems related to TB in countries with high burden of disease, NIH is increasing its focus on persons who also are afflicted with other diseases and conditions, such as HIV, diabetes, and malnutrition.[51]

Malaria

Malaria continues to exact a devastating toll on individuals worldwide, mostly among children in sub-Saharan Africa. Approximately half of the world's population lives in regions at some risk for malaria. Achieving the ultimate goal of ridding malaria from every region of the globe will require three phases: control, elimination and, finally, eradication.

In 2009, NIH joined the Roll Back Malaria (RBM) Partnership in an intensified effort to halve the global malaria burden by 2010, an important milestone on the road to achieving the WHO Millennium Development Goal of reducing malaria deaths to near zero by 2015. NIH supports research on 10 candidate vaccines for malaria, 5 of which are in clinical trials.

Researchers studying basic mosquito biology recently identified genetic markers involved in pyrethroid insecticide resistance; these now are being evaluated for utility in the field.

In 2009, NIH joined the Roll Back Malaria (RBM) Partnership in an intensified effort to halve the global malaria burden by 2010.

A recently launched NIH initiative, the International Centers of Excellence in Malaria Research, supports a global, multidisciplinary approach to understanding malaria in the context of control, elimination, and eradication. Outstanding needs include faster and more reliable ways to diagnose malaria and to identify different parasite species and drug-resistant strains that may emerge, systematic methods for translating basic research into effective treatment and control strategies, and safe and effective therapies to counteract strains of the malaria parasite that have developed resistance to current drugs.

HIV/AIDS

HIV/AIDS continues to devastate communities around the world. Without a vaccine to protect against HIV infection or a cure for HIV/AIDS, new biomedical approaches and behavioral interventions urgently are needed to stop the HIV/AIDS pandemic. NIH conducts and supports research to develop new strategies and methods that prevent the spread of HIV, such as vaccines, microbicides, strategies to prevent mother-to-child transmission, antiretroviral therapy (ART) as a pre-exposure prophylaxis strategy, treatment for drug addiction, and behavioral interventions. The goal of the NIH prevention research agenda is to develop a "toolbox" of scientifically proven prevention strategies that can be tailored to different populations affected by HIV/AIDS around the world.

The ultimate prevention tool—and what is considered the best hope for ending the HIV/AIDS pandemic—is a safe and effective vaccine that can prevent HIV infection. NIH recently renewed its emphasis on basic research in HIV vaccines through two major initiatives.[52] The Basic HIV Vaccine Discovery Research Program, which began in 2008, seeks to generate knowledge to inform new conceptual designs and approaches to HIV vaccines. Through the B Cell Immunology for Protective HIV-1 Vaccine Program, NIH fosters basic immunology research on B cell and antibody regulation as a foundation for the development of new HIV vaccines. In addition, NIH recently launched an exploratory clinical trial through the HIV Vaccine Trials Network (HVTN) to examine whether a two-part vaccine regimen can decrease viral load in vaccinated male study participants who later become infected with HIV.

NIH also is advancing other new approaches in HIV prevention. Two NIH-supported trials recently showed that medically supervised circumcision of adult males markedly reduces the risk of acquiring HIV infection, and that the microbicide gel PRO 2000 was safe and potentially effective in women.[53] Additional studies are evaluating other microbicides—gels, creams, or foams applied to the vagina or rectum—that are designed to prevent HIV and other sexually transmitted infections. Through collaborations with government and nongovernmental partners, NIH also is evaluating an HIV prevention strategy called pre-exposure prophylaxis (PrEP), which involves providing ARV drugs to HIV-negative individuals who are at high risk of HIV infection.[54] Additionally, recent modeling data have shown that universal voluntary, routine HIV testing and immediate treatment of individuals diagnosed with HIV could reduce dramatically the number of new HIV cases in the next decade. This approach is based on the premise that immediate initiation of ARV therapy for those individuals who test positive would lower their viral load in the blood and, thereby, reduce the spread of HIV. NIH is addressing critical research questions to determine the feasibility of this "test and treat" approach.[55]

Aging is an expanding focus of HIV/AIDS research at NIH. HIV/AIDS began its deadly course in the United States mostly as a disease of young men. Today, due to a growing number of cases newly diagnosed in older persons and the advent of potent, multidrug therapy against HIV in the mid 1990s, many HIV-infected Americans are living into their 50s and well beyond. Older adults with long-term or new HIV infection experience complex interactions among HIV, antiretroviral therapy (ART), age-related changes to the body, and, often, treatment for illnesses associated with aging.

NIH supports research on the interaction between HIV and aging in areas as diverse as organ diseases, cancer, bone density, mental health, response to antiretroviral therapy, and immune function. For example, researchers with the Multicenter AIDS Cohort Study (MACS) have shown that HIV infection accelerates the development of frailty, a condition of the elderly that makes people more vulnerable to illness, injury, and death. Scientists now want to determine which HIV-infected individuals are at highest risk for developing HIV-associated frailty, with the hope of identifying factors to mitigate or prevent its development. Individuals who undergo long-term ART frequently experience side effects of disease and treatment that mimic or accelerate aging processes. NIH supports efforts to evaluate emerging issues in HIV clinical care such as the impact of aging on HIV treatment response.[56] NIH recently established a multi-Institute collaboration to solicit research on clinical and translational medical issues in the diagnosis and/or management of HIV infection and its consequences in older people[57] and initiated a prospective study to identify possible long-term adverse outcomes of HIV infection and complications of ART or experimental interventions in HIV-infected infants, children, and adolescents.

NIH also is expanding its efforts to find a cure for HIV/AIDS. Through research to improve basic understanding of HIV latency, NIH seeks to achieve long-term HIV remission following discontinuation of ARV therapy—a "functional" cure—or, ultimately, complete eradication of residual virus. NIH supports research to eliminate HIV reservoirs, pockets of undetectable latent and persistent HIV, which exist even in people on ARV therapy who have an undetectable viral load.

Through research to improve basic understanding of HIV latency, NIH seeks to achieve long-term HIV remission following discontinuation of ARV therapy—a "functional" cure—or, ultimately, complete eradication of residual virus.

To ensure that vulnerable populations benefit from research progress on HIV/AIDS, NIH has launched initiatives to reduce HIV transmission, ensure access to rapid screening tests, and deliver effective treatment. An initiative begun in 2008, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the United States, explores new avenues to prevent and treat HIV disease among drug users. Outreach programs among drug users have helped to reduce HIV/AIDS transmission. NIH also is working to ensure that effective HIV/AIDS treatment reaches the prison population and that inmates, once released, continue to receive effective treatment.[58] A study to determine whether intervention helps reduce risky sexual behaviors among homeless HIV-positive adults indicates that intervention programs focusing on skills development and the physical and mental health needs of participants are more likely to succeed than are programs focused only on reducing HIV transmission.[59] A recent Adolescent Medicine Trials Network for HIV/AIDS (ATN) study documented that HIV-positive adolescents frequently do not follow prescribed treatment regimens, and identified several factors associated with nonadherence to therapy.

NIH also supports initiatives to address the U.S. epidemic in specific racial and ethnic populations. NIH has launched a new initiative to address the serious and complex HIV/AIDS epidemic in U.S. Hispanic populations through community outreach, regional workshops, leadership development, and research collaborations.[60]

NIH is continuing its support of the two largest observational studies of HIV/AIDS in women (Women's Interagency HIV Study) and homosexual or bisexual men (MACS) in the United States.[61] Recent cohort studies focus on aging veterans[62] and more generally on aging, sleep disorders, frailty, renal function, cognitive function, and behavior among HIV-infected persons. NIH also supports two prospective cohort studies of HIV-infected women, HIV-exposed but uninfected children, and HIV-infected children at clinical sites in Latin America (the NICHD International Site Development Initiative Perinatal and Pediatric cohorts). In addition, the Pediatric HIV/AIDS Cohort Study (PHACS) includes an observational study of HIV infection among perinatally infected youth entering adolescence and young adulthood, as well as a study to evaluate the long-term effects of exposure to ARV drugs during gestation on uninfected infants born to HIV-infected mothers.

NIH disseminates research findings and other important information about HIV/AIDS through *AIDS info* and *infoSIDA*, as well as a new initiative to incorporate information from AIDS-related conferences into the NLM Gateway service for public access on the Web.

Emerging Infectious Diseases and Biodefense (including seasonal and other influenzas)

NIH is the lead agency within HHS for conducting and supporting research on potential agents of bioterrorism and emerging infectious diseases that directly affect human health. NIH research to combat naturally occurring diseases overlaps with efforts to address threats posed by the accidental or intentional release of hazardous biological, chemical, or radiological agents. The overriding goal of these research programs is to enable NIH to respond effectively to a public health emergency regardless of its cause. In addition to basic, translational, and clinical research to develop safe and effective medical countermeasures, NIH supports programs to expand research infrastructure and maintain resources such as the Influenza Virus Resource.[63] Biodefense research includes the development of new and improved vaccines and therapeutics against smallpox, anthrax, botulinum toxin, and other potential bioterror agents.

The sudden and unpredictable appearance of 2009 H1N1 influenza is a classic example of an emerging infectious disease.[64] As of October 2009, more than 340,000 people worldwide had confirmed cases of 2009 H1N1 flu and more than 4,100 (1.2 percent) had died. NIH-funded researchers have discovered that the genes of the 2009 H1N1 influenza virus[65] are derived from human flu viruses, avian flu viruses, and swine flu viruses, including the H1N1 virus that caused the 1918 pandemic, which killed 40-50 million people worldwide. In collaboration with Centers for Disease Control and Prevention (CDC) scientists, NIH-funded researchers found that the 2009 H1N1 viruses replicate more efficiently in lung tissue than do seasonal flu viruses. NIH is conducting clinical trials of H1N1 vaccines in adults, children,[66] HIV positive women, and people with asthma, and has initiated the first clinical trial of an H1N1 influenza vaccine in pregnant women.[67]

NIH also is assessing the ability of experimental antiviral drugs to block infection with 2009 H1N1. Researchers are working to develop or refine antiviral drugs and diagnostic tools for both seasonal and pandemic influenza (2009 H1N1) strains. NIH is developing diagnostic platforms than can rapidly identify a wide variety of pathogens in clinical samples, including specific subtypes of influenza. Some of these diagnostics already are being used in clinical settings to help meet the increasing demand for rapid and accurate diagnosis of influenza, including the 2009 H1N1strain. NIH supports a diverse portfolio of basic influenza research with the ultimate goal of developing universal influenza vaccines that can protect against multiple strains of the virus.

Global demand for the 2009 H1N1 vaccine highlighted the urgency of developing new, faster, more efficient methods of vaccine production. Currently, influenza vaccines produced in the United States rely on egg-based manufacturing methods. Influenza vaccines have been prepared in eggs for years, but the process is lengthy and requires hundreds of millions of eggs. Cell culture-based vaccines currently are licensed only in Europe, and it may be some time before vaccines produced using cell cultures are licensed in the United States. NIH actively supports research to improve current influenza technologies and vaccines and develop new ones. Innovative vaccine technologies being developed by NIH and its industry partners include using recombinant DNA to create subunit vaccines in which various influenza virus proteins are selectively produced in cultured cells and are then purified and used in a vaccine; DNA vaccines, in which influenza genetic sequences are used to stimulate an immune response against the proteins coded for by these genetic sequences; and approaches that insert the genes of influenza viruses into a different virus (a “vector”) that is used as a vaccine. These and other “next generation” vaccines must undergo extensive development, safety, and efficacy testing before they can be used, and then will require time to reach commercial levels of manufacturing.

An important facet of preparedness for emerging infectious diseases is the need to protect health care workers. Many workers are at risk for exposure to emerging airborne biological agents, including the 2009 H1N1 influenza virus and other pandemic influenza viruses, *MTb*, and other viruses. Some hospital workers are exposed to accidental releases of

hazardous biological materials due to lack of proper training, engineering controls, handling, storage, or poor maintenance and cleaning of laboratory equipment. With NIH support, the Service Employees International Union (SEIU) has trained almost 500 health care workers, including nurses, in pandemic flu preparedness with a focus on preventing respiratory exposures from all these potential sources.

According to CDC, each year, seasonal influenza is a factor in more than 36,000 deaths in the United States, and 250,000 to 500,000 deaths worldwide.[68] NIH supports research to develop more effective diagnostics, treatments, and preventive measures for seasonal influenza. The Centers of Excellence for Influenza Research and Surveillance (CEIRS) program is expanding its animal influenza surveillance program internationally and domestically, and focuses on high-priority areas in influenza research.[69] The NIH Multinational Influenza Seasonal Mortality Study (MISMS) analyzes national and global mortality patterns associated with influenza virus circulation.[70] NIH participates in the South East Asia Infectious Diseases Clinical Research Network (SEAICRN), which helps its partners develop clinical research capacities and hosts events and training sessions to mitigate outbreaks of influenza and other emerging infectious diseases.

The Centers of Excellence for Influenza Research and Surveillance program is expanding its animal influenza surveillance program internationally and domestically, and focuses on high-priority areas in influenza research.

Biological Countermeasures Research

The NIH biodefense research program has achieved major successes in the development of countermeasures against significant bioterror threats. Some countermeasures are stockpiled or available for emergency use; others in the development pipeline have been transferred to the HHS Biomedical Advanced Research and Development Authority (BARDA) for advanced development. Promising candidate countermeasures in development include ST-246, a smallpox drug candidate that has protected animals from an otherwise lethal exposure to live poxviruses.[71] ST-246 has been used recently under emergency use investigational new drug (E-IND) applications to treat life-threatening complications of vaccinia exposure.[72] Advanced development and production continues for a recombinant protective antigen vaccine for anthrax and a modified vaccinia Ankara vaccine for smallpox.[73]

Advanced development and production continues for vaccines for anthrax and smallpox.

NIH supports partnerships with government, industry, small businesses, and academia to facilitate the development of vaccines and therapeutics against diseases such as botulism and anthrax, as well as against Ebola and Marburg viruses. NIH also supports the development of a nonhuman primate model for plague, which has been useful in studies of three licensed antibiotics for plague.

Chemical Countermeasures

NIH helps coordinate research to develop safe and effective medical countermeasures against chemical weapons. The NIH Countermeasures Against Chemical Threats (CounterACT) Research Network supports the development of medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The network, a collaboration between NIH and the U.S. Department of Defense, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. The network has developed therapeutics for cyanide, nerve agents, chlorine, sulfur mustard, and radiation exposures. Training of personnel remains a critical facet of effective response to a release of chemical or nuclear/radiological material. For the past 15 years NIH has worked with the SEIU to provide high-quality training for hazardous materials emergency responders.

The NIH Countermeasures Against Chemical Threats (CounterACT) Research Network supports the development of medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster.

Nuclear/Radiological Countermeasures

NIH continues to lead HHS efforts to sponsor and coordinate research to develop medical countermeasures to mitigate and/or treat radiation-induced damage.[74] Many candidate medical countermeasures are in the early stages of discovery, including medical countermeasures for hematopoietic acute radiation syndrome (ARS), gastrointestinal ARS, radiation-induced lung pneumonitis and/or fibrosis, and other radiation-induced injuries. Three orally bioavailable forms of diethylenetriaminepentaacetic acid (DTPA) for treating victims with internal radionuclide contamination from fallout, or "dirty bombs," are in development. Other areas of research include characterization of genomic, proteomic, metabolomic, and cytogenetic markers of radiation injury, and development of biodosimetry devices to provide accurate and timely radiation exposure information to assist in medical triage and treatment strategies.[75]

Infrastructure and Research Resources

NIH has invested substantially in the intellectual and physical infrastructure needed to build the Nation's capacity for research on biodefense and emerging infectious diseases.[76] The NIH-funded 11 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research are developing new or improved ways to treat, diagnose, and prevent illnesses including anthrax, plague, and dengue fever. NIH has supported the construction of two National Biocontainment Laboratories. Thirteen NIH-funded Regional Biocontainment Laboratories have BSL-3 capacity.

NIH also supports research resources including databases and data integration services. For example, NIH maintains the Influenza Virus Resource, a database of influenza viral genome sequences that enables researchers worldwide to compare different virus strains, identify genetic factors that determine their virulence, and identify new therapeutic, diagnostic, and vaccine targets.[77] In the spring of 2009, with the rapid emergence of the 2009 H1N1 pandemic, the database received more than 2,200 influenza sequences from CDC and laboratories from 35 countries.

NIH maintains a database of influenza viral genome sequences that enables researchers worldwide to compare different virus strains, identify genetic factors that determine their virulence, and identify new therapeutic, diagnostic, and vaccine targets.

International Collaboration

Controlling infectious diseases not only saves lives but is essential for building a strong global economy and maintaining international stability. NIH participates in efforts including the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and other global initiatives. NIH supports networks of U.S. and international scientists, trains U.S. and foreign investigators to work internationally, and enhances basic biomedical, clinical, and behavioral research capacity and facilities around the world. Partnerships, including those with bilateral and multilateral international partners, industry, and host governments, provide extraordinary opportunities for research on vaccines, drugs, and new diagnostics to benefit local populations where the research is done.

Over the last decade, NIH has expanded significantly its portfolio of international biomedical research and its global collaborations and partnerships. NIH international infectious disease research includes:

- Studies of HIV/AIDS and maternity care in Kenya
- Studies of heterosexually transmitted HIV infections among couples in urban Zambia and Rwanda

- Use of task shifting—delegating tasks, where appropriate, to less specialized health workers—to effect scale-up of HIV treatment services in Zambia
- Human Papillomavirus (HPV) vaccine trials in Costa Rica that validated the ability of virus-like particle vaccines to protect against HPV 16/18 infection[78]
- Assessments of long-term antibiotic treatment for *Chlamydia trachomatis*, a leading cause of blindness in the developing world, through a clinical trial in Ethiopia

Over the last decade, NIH has expanded significantly its portfolio of international biomedical research and its global collaborations and partnerships.

Other NIH international collaborations include the Project Phidisa clinical research project on HIV/AIDS in South Africa, and the NIH International Centers for Excellence in Research (ICER) sites in Mali, Uganda, and India. The ICERs conduct sustained research on malaria, HIV/AIDS, HIV and TB co-infections, and other diseases in areas that bear the highest infectious disease burden.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Basic Research

Solving One of Immunity's Puzzles: NIH scientists recently identified a protein required for the crucial interactions between T and B cells that lead to production of antibodies and long-lasting immunity to infectious diseases. T cells and B cells interact to form cellular centers, where B cells proliferate and produce antibodies to fight off invading microbes. This process is crucial to normal immune function and resistance to infectious disease. Researchers demonstrated that a protein, SAP, mediates interactions between T and B cells. Specifically, the team found that T cells lacking SAP do not bind strongly to the B cells they would otherwise recognize. This in turn prevents B cells from receiving crucial signals they need to help build antibody-secreting cells. This malfunction leads to the poor immune response observed in patients with X-linked lymphoproliferative disease, a rare disorder affecting newborn boys.

→ Qi H, et al. *Nature* 2008;455(7214):764-9. PMID: 18843362. PMCID: PMC2652134.
→ For more information, see http://www.genome.gov/27528397
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E, I) (**NHGRI, NIAID**)

New Program to Focus on Better Defining Human Immune Profiles: In 2009, NIH requested applications for a new research program designed to build on recent advances in immune profiling to measure the diversity of human immune responses to infection or vaccination. Grantees will use a variety of modern analytical tools that will define molecular signatures of specific infections, vaccines, or immune adjuvants, as well as describe steady-state human immune status by

a number of parameters. This program is a critical component of the NIH immunology research portfolio. This initiative supports studies that characterize human immune cells and their products isolated from diverse subsets of the population after vaccination, infection, or treatment with adjuvants. NIH will create a grantee consortium that will develop and manage a comprehensive database that consolidates and disseminates information for the scientific community and develop new assays and bioinformatics tools to facilitate productivity. This program, originally intended as an FY 2011 initiative, began 1 year early with ARRA funding.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-040.html
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIAID**) (ARRA)

Microbial Genomics: NIH has made significant investments in large-scale, whole-genome sequencing of pathogens over the last decade. NIH also provides comprehensive genomic, bioinformatic, and proteomic resources and reagents to the scientific community:

- The NIH Genome Sequencing Centers of Infectious Diseases rapidly produce high-quality genome sequences of human pathogens and invertebrate vectors of diseases. Over the last decade, NIH has supported large-scale, whole-genome sequencing of pathogens and vectors. Thousands of bacteria, fungi, parasites, invertebrate vectors of diseases, and viruses have been sequenced, including pathogens that cause anthrax, influenza, aspergillosis, TB, gonorrhea, chlamydia, and cholera. For example, more than 3,733 human and avian influenza isolates have been sequenced including almost 500 for H1N1 (as of December 2009).
- The Pathogen Functional Genomics Resource Center generates and distributes genomic data sets, reagents, resources, bioinformatic analysis tools, and technologies for functional analysis of pathogens and vectors.
- Clinical Proteomics Centers for Infectious Diseases and Biodefense apply state-of-the art proteomics technologies for the discovery, quantification, and verification of protein biomarkers in infectious diseases. These data are released to the scientific community and may aid in the production of vaccines, diagnostics, and therapeutics.
- Systems Biology Centers for Infectious Diseases bring together a diverse group of scientists to analyze, identify, quantify, model, and predict the overall dynamics of microbial organisms' molecular networks and their host interactions using both computational and experimental methodologies.

→ For more information, see http://www3.niaid.nih.gov/topics/pathogenGenomics/default.htm
→ This example also appears in Chapter 3: *Genomics*
→ (E/I) (**NIAID**)

Vaccine Research: NIH scientists developed innovative technology that enabled vaccines to virtually eliminate *Haemophilus influenzae* type B meningitis as the leading cause of acquired intellectual disability in the United States. Researchers now are applying this technology to develop a malaria vaccine that prompts an individual's immune system to eliminate the infectious malaria parasite, Plasmodium, from mosquitoes. Using more conventional methods, NIH scientists are testing a new anthrax vaccine made with a purified protein. This vaccine will enable researchers to measure and determine the minimum level of protein needed to confer protection and minimize side effects, compared to the existing anthrax vaccine.

→ (I) (**NICHD**, NIAID, NIDDK)

Antimicrobial and Prebiotic Activity of Oligosaccharides: After lipids and galactose, oligosaccharides comprise the third most prevalent component of human milk. Oligosaccharides are composed of sugar molecules, linked together in short chains in hundreds of combinations. However, oligosaccharides are non-nutritive for human infants. Evidence is accumulating that the reason for the evolutionary persistence of large amounts of oligosaccharides in human milk is because of their antimicrobial properties. These findings appear to signal the advent of a new class of antimicrobial agents

that could be used to prevent bacterial and viral infections of the gastrointestinal tract. NIH now is supporting research to shed light on how oligosaccharides can prevent enteric infections and to use oligosaccharides to help prevent or treat infections. A key step in reaching this goal is to develop biosynthetic means of producing large enough quantities of oligosaccharides with antimicrobial properties for preclinical tolerance and safety studies and for safety and clinical testing in populations that are exposed to gastrointestinal pathogens.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-004.html
→ (E) (**NICHD**)

Tackling Neglected Tropical Diseases: Neglected tropical diseases (NTDs) such as lymphatic filariasis, schistosomiasis, leishmaniasis, and dengue take a tremendous toll on global health. The World Health Organization estimates that more than 1 billion people—approximately one-sixth of the world's population—suffer from at least 1 NTD. NIH scientists and NIH-supported researchers in countries where NTDs are widespread are developing vaccines and treatments for diseases such as leishmaniasis and identifying new drugs for sleeping sickness and Chagas' disease. NIH-supported researchers also have made a significant leap forward in the battle against schistosomiasis by identifying potential new therapies through the use of genomics and medicinal chemistry. The Vector Biology Research Program supports research on several vectors that transmit agents of NTDs. Through this program, a project in French Polynesia aims to reduce populations of *Aedes polynesiensis*, a mosquito species responsible for spreading filariasis. Other investigators studying the mosquito immune response against filarial worms hope to identify targets for blocking development of the worm inside the mosquito. NIH scientists studying the salivary proteome of NTD vectors are identifying novel biologically active compounds and vaccine targets. In FY 2009, NIH-supported researchers reported the first complete genome sequences for two parasite species that cause schistosomiasis. Finally, a public-private partnerships for product development program is designed to accelerate research and development of new diagnostic, preventive, therapeutic, and control strategies for infectious diseases of global importance for which commercial markets currently provide insufficient incentive for corporate investment.

→ For more information, see http://www3.niaid.nih.gov/topics/tropicalDiseases/default.htm
→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/schisto_genomes.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAID**)

Bone Marrow Stromal Cells Help Fight Sepsis: Sepsis is a serious medical condition that affects 18 million people per year worldwide, and is characterized by a generalized inflammatory state caused by bacterial infection. Widespread activation of inflammation and blood clotting pathways leads to multiple organ failure, collapse of the circulatory system (septic shock), and death. In the last few years, it has been discovered that bone marrow stromal cells (BMSCs, also known as mesenchymal stem cells) are potent modulators of immune responses. In this study, BMSCs were administered before or shortly after inducing sepsis by puncturing the intestine to determine whether BMSCs injected into the circulation would have a beneficial effect in preventing or attenuating septic shock. Infusion of BMSCs significantly decreased sepsis-induced mortality and increased organ function in an animal model. The effects appear to be mediated by the production of Prostaglandin E2 when BMSCs are activated during the early stages of sepsis. Prostaglandin E2 subsequently induces the recipient's macrophages to produce substantially more IL-10, a factor that dampens the inflammatory response, which if left unabated, leads to death. This is the first determination of a mechanism by which BMSCs modulate the immune response in an animal model of sepsis. As many people die of sepsis annually as die from heart attacks. A new treatment or preventative regimen desperately is needed. Since the animal model suggests that the BMSCs need not be isolated from the same individual as will receive them, it is possible that cells isolated from nonrelated donors could be prepared and stored for use in patients with high risk for sepsis.

→ Nemeth K, et al. *Nat Med* 2009;15(1):42-9, PMID: 19098906. PMCID: PMC2706487.
→ For more information, see http://www.nature.com/nm/journal/v15/n1/abs/nm.1905.html

→ This example also appears in Chapter 3: *Molecular Biology* and Basic Research and Chapter 3: *Technology Development*
→ (I) (**NIDCR**)

Metabolic Network Model of a Human Oral Pathogen: The bacterium *Porphyromonas gingivalis* causes severe, chronic periodontal disease. Recently NIH-supported researchers constructed a complex metabolic network map for *P. gingivalis* with which to model the metabolic properties of all genomically identified components of the system. The scientists used a technique known as flux-balance analysis (FBA) to construct the model, which consisted of 679 metabolic reactions involving 564 metabolites. There was significant correlation between the model's predictions and the bacterium's experimentally observed metabolism. The true power of this model became apparent when "virtual knockouts" were employed to predict the effect of the loss of certain genes or metabolic pathways on growth rate, and the model very effectively predicted disturbances affecting biosynthesis of large molecules known as lipopolysaccharides. This is the first description of a model of this type for an oral periodontal pathogen. Still in their infancy, metabolic network models are a logical extension of genome sequence data. They can provide the ability to perform virtual metabolic modeling of organisms with limited or no in vivo experimental histories. These models also could be applied to highly interdependent mixed microbial communities, including the oral microbiome, ultimately resulting in new biomedical applications. Such modeling greatly increases opportunities to discover new antibacterial drug targets. These studies provide new molecular targets for therapeutic drugs; they also can suggest the molecular mechanisms for virulence, intracellular persistence and survival, and ability of the bacteria to survive stresses from the (in this case, human) host defense mechanisms.

→ Mazumdar V, et al. *J Bacteriol* 2009;191(1):74-90. PMID: 18931137. PMCID: PMC2612419.
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NIDCR**)

Major Infectious Diseases

Transforming TB Research: Diagnosis, treatment, and control of tuberculosis (TB) increasingly are complicated by the HIV/AIDS co-epidemic and the emergence of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB. NIH is pursuing six critical areas for additional investigation: (1) new TB diagnostic tools; (2) improved therapies for all forms of TB; (3) basic biology and immunology of TB; (4) MDR TB and XDR TB epidemiology; (5) clinical management of MDR TB and XDR TB in people with and without HIV infection, including children; and (6) TB prevention, including vaccines. Recent NIH advances in TB research include:

- Two FDA-approved drugs are found to work in tandem to kill laboratory models of *Mycobacterium tuberculosis* (Mtb) strains, the bacterium that causes TB. The drugs—meropenem and clavulanate—are used to treat other bacterial diseases. A clinical trial is being developed to test the combination in people who have XDR TB.
- New information on the pharmacology of existing and new anti-TB compounds may facilitate the development of improved treatment regimens for adults and children.
- Clinical trials have shown that the immune systems of children who are HIV-infected do not respond well to the current TB vaccine, BCG.
- Clinical trials also have shown that mortality among TB patients co-infected with HIV is reduced drastically when antiretroviral therapy is provided at the same time as TB therapy. Additional studies are underway to determine optimal strategies for the prevention, treatment, and diagnosis of TB in the setting of HIV infection.

Several NIH-supported academic institutions, public-private partnerships, and commercial entities are developing rapid tests for early detection of all forms of TB, including MDR and XDR TB.

→ For more information, see http://www3.niaid.nih.gov/topics/tuberculosis
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAID**)

Development and Testing of Malaria Vaccines and Therapeutics: NIH supports recent calls to work toward the goal of malaria eradication. Means toward this end include stopping the spread of the malaria parasite, reducing the burden of disease region by region, and eliminating the parasite from malaria-endemic countries and then from every country throughout the world. In FY 2008, NIH assessed its malaria research portfolio and identified opportunities for the next phase of malaria research. This led to the publication of the Strategic Plan for Malaria Research and the related NIAID Research Agenda for Malaria. NIH recently launched a new initiative, the International Centers of Excellence in Malaria Research, to support a novel, global, multidisciplinary approach to understanding malaria in the evolving context of control, elimination, and eradication. NIH researchers recently began clinical investigations to assess malaria biology and pathogenesis with collaborators in Mali and Cambodia, activities that resulted in the completion (or expansion) of research facilities and hospitals to support new malaria research programs. Examples of NIH-supported advances in malaria research include:

- Successfully decoding the genome of the parasite that causes relapsing malaria and determining that the anti-malarial drug, chloroquine, may once again be used to prevent malaria in African children.
- Investigating novel vaccine strategies, such as those that block transmission of the malaria parasite to the mosquito vector, and exploring the molecular biology of the parasite and its interaction with humans.

Ten vaccine candidates currently are in preclinical development and five are in clinical trials.

→ For more information, see http://www3.niaid.nih.gov/topics/Malaria/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAID**)

Guidelines for the Medical Management of HIV: HHS issues Federal guidelines for the medical management of HIV infection and its associated co-infections, including antiretroviral treatment of HIV disease, prevention and treatment of opportunistic infections, and prevention of mother-to-child transmission of HIV. The guidelines are written, reviewed, and updated by working groups of the NIH OAR Advisory Council made up of HIV experts from across the country, including physicians, pharmacists, researchers, and community representatives. The guidelines represent the state of knowledge regarding the medical management of HIV disease in the United States. As the introduction and/or availability of new therapeutic agents, new clinical data, and emerging disease threats may change therapeutic options and preferences rapidly, the guidelines are updated frequently and are available as a "living document" on the AIDS*info* website. Updates that recently were added to the AIDS*info* website include the *FDA Alert: Use of Antivirals Tamiflu and Relenza in Children* and the *CDC Interim Guidance-HIV-Infected Adults and Adolescents: Considerations for Clinicians Regarding Novel Influenza A (H1N1) Virus*.

→ This example also appears in Chapter 3: Health Communication and Information Campaigns and Clearinghouses
→ (O) (**OAR**)

HIV Topical Microbicides: Topical microbicides are small molecule prophylactic treatments to prevent the transmission and spread of HIV. Guided by the NIAID Topical Microbicide Strategic Plan, NIH is funding a number of microbicide research studies through the Microbicide Trials Network (MTN), the HIV Prevention Trials Network (HPTN), and the Microbicide Innovation Program (MIP). The microbicides under investigation are designed to prevent HIV transmission by killing or inactivating microbial pathogens, strengthening the body's normal defenses, blocking attachment of HIV to susceptible cells, and preventing HIV from spreading to other uninfected cells. Microbicides typically are administered via a gel, foam, or cream intended to prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically inside the vagina or rectum. In February 2009, NIH-supported researchers found that an investigational vaginal gel called PRO 2000, intended to prevent HIV infection in women, is safe and approximately 30 percent effective (33 percent effectiveness would have been considered statistically significant). While additional data are needed to

determine if PRO 2000 protects women from HIV infection, it was the first human clinical study to suggest that a microbicide may prevent male-to-female sexual transmission of HIV infection.

- → For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/prevention/research/Microbicides/research.htm
- → For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/HPTN_035_gel.htm
- → This example also appears in Chapter 3: *Clinical and Translational Research*
- → (E) (**NIAID**, NICHD, NIMH)

HIV/AIDS Epidemiological and Long-Term Cohort Studies: NIH continues its support of the largest HIV/AIDS observational studies in the United States, the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) of homosexual and bisexual men. These studies repeatedly have made major contributions to our understanding of HIV transmission, disease progression, and best treatment practices. The WIHS, now in its 16th year of research, studies the natural history of HIV infection and AIDS progression in 2,404 HIV-infected and uninfected women, and bridges the gap between theoretic benefits and sustainable gains of antiretroviral therapy. The MACS, now in its 26th year of research, studies the natural history of HIV infection and AIDS progression in 6,973 homosexual and bisexual men at sites located in Baltimore, Chicago, Pittsburgh, and Los Angeles. These domestic cohorts are on the forefront of research to define the clinical manifestations of long-term HIV/AIDS infection. Data from these cohorts have resulted in published studies on the long-term risk of HIV/AIDS on cardiovascular disease. Studies have been initiated on aging, sleep disorders, frailty, renal function, cognitive function, and behavior among HIV-infected persons.

- → For more information, see http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm
- → This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- → (E) (**NIAID**, NCI, NCRR, NICHD, NIDA)

Intervention Reduces Risky Sexual Behavior Among Homeless HIV-Infected Adults: HIV infection in the United States is found more commonly among populations with significant life stressors, such as homelessness and drug use. An NIH-funded program (the Healthy Living Program) already shown to reduce risky sexual and substance abuse behavior among HIV-infected adults also appears to be effective in improving the lives of HIV-infected homeless or near-homeless adults. The program consisted of three intervention modules of five sessions each, designed to help participants reduce risky sexual behaviors and drug use, improve their quality of life, and sustain healthy behaviors. Compared with a control group who did not receive the Healthy Living Program intervention, individuals who were homeless or near-homeless in the 3 years prior to and during the study and who participated in the intervention engaged in 34 percent fewer risky sexual acts and 72 percent fewer sexual encounters with partners who were not infected with HIV or were of unknown HIV status. The study's results highlight the importance of programs designed to prevent or reduce the spread of HIV among people in high-risk populations. They also indicate that intervention programs focusing on skills development and including the physical and mental health needs of participants, are more likely to succeed than programs focusing only on reducing HIV transmission.

- → Rotheram-Borus MJ, et al. *Am J Public Health* 2009;99(6):1100-7. PMID: 18799777. PMCID: 2679793.
- → For more information, see http://www.nimh.nih.gov/science-news/2008/intervention-helps-reduce-risky-sexual-behavior-among-homeless-hiv-positive-adults.shtml
- → This example also appears in Chapter 3: *Clinical and Translational Research*
- → (E) (**NIMH**)

OAR Management and Coordination of the Trans-NIH HIV/AIDS Research Portfolio and Budget: NIH supports a comprehensive program of basic and clinical biomedical and behavioral research on HIV infection and its associated comorbidities, co-infections, opportunistic infections, malignancies, and other complications. OAR plans and coordinates all NIH AIDS research, including formulation of the NIH AIDS research budget. Through its unique, trans-NIH planning,

budgeting, and portfolio assessment processes, OAR ensures that NIH AIDS research dollars are invested in the highest priority areas of scientific opportunity. Each year, OAR develops the *Trans-NIH Plan for HIV-Related Research* in collaboration with scientists from NIH, other government agencies, academia, and foundations, as well as community representatives. During the process, the state of the science is reviewed, newly emerged and critical public health needs are assessed, and scientific opportunities are identified. The Plan serves as the framework for developing the annual AIDS research budget for each IC, determining the use of AIDS-designated dollars, and tracking and monitoring all NIH AIDS and AIDS-related research expenditures. The trans-NIH AIDS research budget, developed by the OAR Director in conjunction with the ICs, is explicitly tied to the objectives of the Plan. This process reduces redundancy, promotes harmonization, and assures cross-Institute collaboration. OAR also is required to prepare an annual Presidential bypass budget based solely on scientific opportunities.

→ (O) (**OAR**)

OAR Management and Coordination of Trans-NIH HIV/AIDS Research to Address the AIDS Epidemic in the United States: Every nine and a half minutes, someone in the United States is infected with HIV. It is estimated that in 2006, 56,300 people were newly infected with the virus. There are large disparities in the prevalence of HIV among different racial and ethnic populations. Black men and women, Hispanic men, and men who have sex with men of all races are impacted disproportionately by HIV. In 2006, blacks accounted for 45 percent of new infections and Hispanics for 17 percent, even though those populations comprised only 13 percent and 15 percent, respectively, of the U.S. population at that time. Moreover, the prevalence rate for black men was six times the rate for white men, and the rate for Hispanic men was more than twice that for white men. OAR leads the trans-NIH planning and coordination efforts in the area of AIDS research in racial and ethnic populations. A section of the annual Trans-NIH Plan for HIV-Related Research is specifically dedicated to research in this area. The Plan, developed in collaboration with scientific experts and community members, serves as a roadmap for the planning of AIDS-related research in this area. OAR also supports a multifaceted initiative to address the U.S. epidemic, particularly in racial and ethnic populations. For example, OAR has launched a new initiative to address the serious and complex AIDS epidemic in U.S. Hispanic populations through community outreach, regional workshops, leadership development, and research collaborations. In addition, OAR, in collaboration with NIAID and the NIH CC, has provided key support for a new trans-NIH initiative on AIDS in the District of Columbia, a city with large black and Hispanic populations and where 3 percent of the population is known to be infected with HIV.

→ Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2007. Vol. 19. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2009. Available at www.cdc.gov/hiv/topics/surveillance/resources/reports/. Accessed July 14, 2009.
Centers for Disease Control and Prevention. HIV Prevalence Estimates—United States, 2006. MMRW. 2008; 57(39);1073-1076. Available at www.cdc.gov/mmwr/preview/mmwrhtml/mm5739a2.htm. Accessed July 14, 2009.
→ For more information, see http://www.oar.nih.gov/strategicplan/fy2010/pdf/Chapter5.pdf
→ For more information, see http://www.nineandahalfminutes.org
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (O) (**OAR**)

OAR-Sponsored Initiatives Targeting Scientific Needs in AIDS Research: OAR, located within the NIH Office of the Director, identifies scientific areas that require focused attention and manages and facilitates multi-Institute and trans-NIH activities to address those needs. OAR fosters this research through a number of mechanisms, such as designating funds and supplements to jump-start or pilot program areas, and sponsoring reviews or evaluations of scientific programs. OAR, alone or in collaboration with NIH ICs, also frequently convenes scientific workshops and conferences, bringing together leading researchers from around the world to review the state-of-the-science and recommend new cutting-edge initiatives. The success of these initiatives is the expansion and/or realignment of the research portfolio in targeted areas. In addition, OAR convenes meetings of the OAR Advisory Council to focus on critical scientific research areas to highlight current trans-NIH efforts and seek advice and guidance on new avenues or approaches to move the science forward. Areas

recently addressed by OAR include microbicides, nutrition and the clinical management of HIV/AIDS, genomics and the host response to HIV, human immunology, the domestic AIDS epidemic, and HIV-prevention interventions for women.

→ (O) (**OAR**)

Recruiting for HIV Research Using Mobile Vaccine Units: Evaluating the safety of candidate vaccines and treatments in humans depends on trust and partnership among scientists, clinicians, and study volunteers. NIH is reaching out to District of Columbia (DC)-area communities to raise awareness among diverse groups about HIV/AIDS. The mobile clinic is an extension of the vaccine clinic of the NIH Vaccine Research Center (VRC). The mobile clinic facilitates collaboration among scientists, clinicians, and study volunteers by raising awareness about HIV vaccines and by improving access for volunteers. With its new mobile clinic, the VRC enhances this vital collaboration by improving access for people in the DC metropolitan area who volunteer for clinical research studies to help find vaccines for HIV/AIDS and other infectious diseases. The mobile clinic can expand NIH outreach and recruitment efforts to neighborhoods in Baltimore and Frederick, Maryland, as well as DC and its suburban neighbors. The unit made its first community appearance in June 15, 2008, at the 33rd annual Capital Pride Festival (a signature event held by the lesbian/gay/bisexual/transgender community).

→ For more information, see http://nihrecord.od.nih.gov/newsletters/2008/07_25_2008/story4.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (I) (**NIAID**)

Renewed Focus on Basic HIV Vaccine Discovery Research: In March 2008, NIH sponsored a Summit on HIV Vaccine Research and Development. Participants reached consensus that NIH should increase its emphasis on basic vaccine discovery research. Toward this end, the Highly Innovative Tactics to Interrupt Transmission of HIV program was established to stimulate research on novel, unconventional, "outside the box," high-risk, high-potential, and high-impact approaches that might provide long-term protection from HIV acquisition. The Basic HIV Discovery Research initiative also was initiated to support generation of knowledge that will inform new conceptual approaches to HIV vaccine design. NIH also funds new research through the B Cell Immunology for Protective HIV-1 Vaccine program to foster fundamental research on B cell immunology to derive new understanding and approaches for development of HIV vaccines. NIH continues to conduct clinical research as appropriate and seeks to answer basic research questions through clinical trials. NIH recently launched an exploratory clinical trial through the HIV Vaccine Trials Network to examine whether a two-part vaccine regimen can decrease viral load in vaccinated male study participants who later become infected with HIV. It is hoped that this study will answer important scientific questions that could lead to the discovery and development of new and improved HIV vaccine candidates.

→ For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/research/
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-024.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAID**) (GPRA)

Support for Research on the Dissemination, Implementation, and Operation of HIV Preventive Interventions: NIH continues to support research on all aspects of HIV preventive interventions. While effective preventive interventions have been developed, there is a recognized gap between their development and their later uptake by community-level service providers. In FY 2008, NIH issued a funding opportunity announcement (FOA) to encourage research ensuring that these interventions are adopted and effectively implemented. The FOA invites applications for research projects that will enhance technology transfer, dissemination, implementation, and operational research related to evidence-based HIV preventive interventions. Staff from NIH and the Centers for Disease Control and Prevention collaborated in the development of this FOA by identifying research gaps and opportunities in these areas. Five categories of projects, in

particular, were identified in which additional research activities could assist in the effective and efficient implementation of HIV preventive interventions: dissemination strategies, adoption of interventions, implementation fidelity and adaptation, intervention effectiveness, and sustainability of interventions.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-166.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIMH**, CDC, NICHD, NINR)

Three-Pronged Approach to Fighting HIV: The unique and formidable challenge of combating HIV is spurring leaders in medicine and public health to consider a bold new approach to fighting it. NIH and other organizations are exploring a three-pronged approach to fight the HIV/AIDS pandemic. The first prong is pre-exposure prophylaxis (PrEP), which uses antiretroviral therapies to prevent HIV infection among people who are not infected with HIV but who are at high risk of becoming infected. NIH currently is testing this approach in clinical trials such as the iPREX study, which is examining whether the HIV treatment Truvada can prevent HIV infection among HIV-negative men who have sex with men. The second prong is a novel approach, based on mathematical modeling, which suggests that the implementation of a universal HIV testing program and the immediate initiation of antiretroviral therapy (ART) for those individuals who test positive could dramatically reduce the number of new HIV cases within the decade. NIH now is addressing a number of critical scientific issues to determine the feasibility of this approach. Finally, NIH is strongly encouraging research to cure HIV by eliminating HIV reservoirs, pockets of undetectable latent and persistent HIV, which exist even in people on ART who have an undetectable viral load. Stopping ART treatment results in a rebound of viral load to levels seen prior to treatment. NIH has launched a new initiative to identify these reservoirs and develop techniques to eradicate them.

→ Paltiel AD, et al. *Clin Infect Dis* 2009;48(6):806-15. PMID: 19193111.
Dieffenbach CW, Fauci AS. *JAMA* 2009;301(22):2380-2. PMID: 19509386.
→ For more information, see http://www.washingtonpost.com/wp-dyn/content/article/2009/04/15/AR2009041503040.html
→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/test_treat.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAID**) (ARRA)

OHARA: The Oral HIV/AIDS Research Alliance: At the vanguard of basic, translational, and clinical research to combat the oral manifestations of HIV/AIDS is the NIH-funded Oral HIV/AIDS Research Alliance (OHARA), which drives and supports novel clinical studies in the United States and internationally to improve diagnosis, treatment, and management of comorbidities of AIDS-related oral complications, including necrotizing ulcers and tumors, fulminating fungal infections, and painful viral lesions that occur in almost all 33 million people infected worldwide. Their devastating effects compromise nutrition and exacerbate immune suppression in addition to the local effects. Even since the advent of antiretroviral therapy (ART), oral complications of AIDS remain a major public health problem. Though ART alleviates some symptoms, many oral lesions need additional specific treatment and globally, only 30 percent of HIV-infected individuals for whom ART is indicated receive it. The estimated prevalence of U.S cases of HIV/AIDS in 2006 exceeded 1.1 million, while about 56,300 people were newly infected with HIV that year. In its fourth year OHARA is making significant strides for people living with HIV/AIDS. OHARA is formed by world-expert scientists and clinicians. Its success is driven by three geographically and academically separate core units that provide expertise in epidemiology, mycology, and virology, embraced by a centralized NIH management and leadership. Currently, OHARA has ramped up eight clinical studies in various phases. They include studies to assess the clinical effectiveness of diagnostic tools for HIV/AIDS-related conditions, and compare the safety and efficacy of novel treatments and preventive strategies for HIV/AIDS-related oral diseases and malignancies.

→ Shiboski CH, et al. *J Oral Pathol Med* 2009;38(6):481-8. PMID: 19594839.
Jacobson MA, et al. *PLoS One* 2009;4(4):e5277. PMID: 19381272. PMCID: PMC2667217.
→ For more information, see http://aactg.org/committees/scientific/optimization-co-infection-and-co-morbidity-management/subcommittees/ohara-sub-3

→ For more information, see http://www.nidcr.nih.gov/Research/DER/IntegrativeBiologyAndInfectiousDiseases/AIDSImmuno.htm
→ For more information, see http://aactg.org/about-actg
→ For more information, see http://www.who.int/hiv/data/en/
→ For more information, see http://www.cdc.gov/hiv/topics/surveillance/basic.htm#Main
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDCR**, NIAID)

Understanding HIV, TB, and Malaria Co-infection: Tuberculosis (TB) is one of the leading causes of death among people living with HIV/AIDS and one of the most common opportunistic infections they experience. HIV and TB reinforce one another: HIV activates dormant TB in a person, who then becomes infectious and able to spread the TB bacillus to others. HIV infection increases the risk of getting TB by a factor of 20 or more, according to the World Health Organization. Similarly, many HIV-positive individuals are co-infected with malaria and face poorer treatment outcomes for both diseases. Notably, malaria infection in pregnant HIV-positive patients leads to worse outcomes for both the mother and the child. NIH is increasing its focus on TB co-infection with HIV, malaria, and other pathogens. Questions addressed include when to start antiretroviral therapy (ART) in patients co-infected with HIV and TB and how best to prevent development of active TB disease in HIV-infected individuals who are receiving ART. Other studies attempt to develop new diagnostics and TB treatments for individuals co-infected with TB and HIV. In addition, several studies underway assess how best to treat women and children with HIV and either TB or malaria. Finally, the Children with HIV and Malaria Project, a prospective, longitudinal study of Ugandan children, is designed to determine if HIV increases the risk of malaria in children, whether malaria is associated with accelerated HIV disease progression, if malaria treatment has a higher failure rate in HIV-infected children in comparison with HIV-uninfected children, and whether trimethoprim-sulfamethoxazole prophylaxis increases incidence of resistant malaria. The study enrolled 300 children with more than 3 years of follow-up, and concluded in September 2009.

→ For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/therapeutics/intro/drug_discovery.htm
→ For more information, see http://www3.niaid.nih.gov/topics/tuberculosis/
→ For more information, see http://www.who.int/entity/tb/challenges/hiv/tbhivbrochure.pdf
→ For more information, see http://www.unaids.org/en/policyandpractice/hivtreatment/coinfection/tb/default.asp
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIAID**)

Microbiome of the Lung and Respiratory Tract in HIV: Research grant applications were solicited in 2009 for studies to characterize the lung and respiratory tract microbiota in HIV-infected individuals and matched HIV-uninfected controls, using molecular and high-throughput techniques to identify bacteria and other organisms, including viruses, cell-wall deficient organisms, protozoa, and fungi. The characteristics and mix of organisms populating the respiratory tract, coupled with the state of local respiratory defenses, are key factors in determining whether a person remains healthy or develops infection. HIV-infected individuals are at very high risk of developing pneumonias caused by pathogenic and opportunistic microorganisms. These respiratory infections frequently cause morbidity, and they often are life-threatening. They also may increase the rate of replication of HIV, accelerating the course of HIV disease. HIV-infected individuals often experience decreased lung function following pneumonia which is not observed in normal, HIV-uninfected populations. Furthermore, lung infections and microbial colonization are suspected in the etiology of HIV-associated emphysema and pulmonary hypertension. Lung infections also may play a role in inducing the immune reconstitution syndrome seen in some HIV-infected patients following initiation of multidrug antiretroviral regimens. Knowledge of the role of the lung microbiome in preserving health or causing disease and the divergent effects observed in HIV-infected vs. uninfected individuals may lead to the identification of predictors of disease progression and therapeutic targets for translation into better preventive and treatment strategies.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-006.html

→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NHLBI**)

Stimulating Transformative Research in HIV/AIDS: In recent years, widespread public education campaigns in the United States have fueled progress in reducing HIV/AIDS transmission that occurs through the sharing of injection equipment among drug users. However, transmission through high-risk sexual contact is on the rise—these behaviors often are exacerbated by substance abuse and ensuing altered judgment. To achieve a more comprehensive approach to this problem, NIH initiated its Avant-Garde Award series in 2008, with the goal of stimulating high-impact research from varied scientific disciplines to pave new avenues of treatment for HIV disease and prevention of new HIV infections among drug abusers. This award, modeled after NIH's Pioneer Award, provides funds of up $0.5 million per year for 5 years and uses interviews with prospective candidates to more fully discern the scientist's and project's potential. One exemplary awardee is evaluating the effectiveness of expanding highly active antiretroviral treatment (HAART) coverage among injection drug users as a population-level HIV prevention strategy. A second is focusing on the ability of HIV to hijack key proteins involved in the regulation of host cell gene expression. A second initiative, the AIDS-Science Track Award for Research Transition (A-START), facilitates the entry of newly independent and early career investigators into the area of drug abuse and HIV/AIDS, an identified area of research need. Examples of projects supported through this mechanism include research on: (1) statistical models to explain ethnic disparities in HIV/AIDS among drug users, and (2) effects of morphine on immune responses to a candidate HIV vaccine in a primate model.

→ For more information, see http://www.cdc.gov/hiv/topics/surveillance/incidence.htm
→ For more information, see http://www.drugabuse.gov/about/organization/arp
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**)

Rapid HIV Testing Clinical Trial: HIV testing is an important component of HIV prevention. To help prevent late diagnosis and HIV spread, NIH is working to identify and address the cultural barriers to making HIV screening more acceptable and to strengthen the link between education, testing and counseling, and treatment within all ethnic groups. NIH-supported modeling research has shown that routine HIV screening, even among populations with prevalence rates as low as 1 percent, is as cost-effective as screening for other conditions such as breast cancer and high blood pressure. Still, little is known about whether offering testing in the absence of counseling influences patient acceptance or how they receive results. How and whether testing absent counseling influences HIV risk behaviors among those who are HIV negative also remains to be determined. Indeed, the Institute of Medicine has recommended comparison research to include significant prevention counseling as a key variable. In this regard, a randomized controlled clinical trial—taking place in NIH's Drug Abuse Treatment Clinical Trials Network—is recruiting individuals receiving drug abuse treatment to participate in a multicenter HIV testing and counseling study. The study will assess the relative effectiveness of on-site HIV rapid testing with brief, participant-tailored prevention counseling as compared with (1) on-site testing with information only and (2) referral for off-site HIV testing. HIV screening has important public health implications, recognized by the Centers for Disease Control and Prevention, which has called for increased HIV screening as part of its recommended guidelines. NIH is eager to advance new HIV rapid-screen technologies and counseling in community drug treatment programs and in criminal justice settings.

→ For more information, see http://www.drugabuse.gov/about/organization/arp
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0032.html
→ For more information, see http://www.drugabuse.gov/about/organization/arp
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**)

Multicenter AIDS Study (MACS) Small Grant Opportunity: MACS is an ongoing (since 1984) epidemiological study in several U.S. cities of multi-ethnic/racial HIV-infected and HIV-uninfected men who have sex with men (MSM). A small grant funding opportunity is enhancing the value and potential for new knowledge from the MACS by examining drug use and HIV/AIDS among MSM over the life course. Studies will include an examination of social and behavioral risk factors and trajectories, the role of drug use in neurocognitive function, and other medical consequences. Findings from these studies may lead to new insights and interventions targeting this high-risk group. Such findings reinforce the importance of implementing interventions targeting drug reduction as part of comprehensive and efficacious HIV prevention program.

→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: Clinical *and Translational Research*
→ (E) (**NIAID**, NIDA, NIMH)

Getting Proven Treatments into the Criminal Justice System: Unfortunately, most inmates in need of substance abuse treatment do not receive it while in prison and, upon their release, continue a vicious cycle of drug use and crime. In response, NIH—along with multiple Federal agencies and health and social service professionals—is working systematically to move science-based treatment interventions into the criminal justice system, where they can have a major impact. In a Delaware Work Release study, those who participated in prison-based treatment followed by aftercare were 7 times more likely to be drug free after 3 years than those who received no treatment. Other research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) affirms the critical need for prisoners to receive effective substance abuse treatment while incarcerated and during their re-entry into the community. A recent randomized clinical trial found that prisoners who began methadone maintenance treatment in prison were significantly more likely after 12 months post-release to continue treatment and decrease drug use and criminal activity than a counseling-only group. A related issue for this population is heightened HIV risk—the U.S. prison system also being where many inmates first receive HIV testing and initiate treatment. However, only a nominal percentage continues this treatment following release. New research shows that simply providing formal assistance in filing the paperwork for antiretroviral treatment medications can promote greater continuity of HIV pharmacotherapy among released inmates. Gaining insight into ways to reduce drug use and criminal recidivism—including among adolescents for whom the same issues apply—as well as limit HIV spread in communities means huge economic and social cost savings.

→ Baillargeon J, et al. *JAMA* 2009;301(8):848-57. PMID: 19244192.
Chandler RK, et al. *JAMA* 2009;301(2):183-90. PMID: 19141766. PMCID: PMC2681083.
Kinlock TW, et al. *J Subst Abuse Treat* 2009;37(3):277-85. PMID: 19339140. PMCID: PMC2803487.
Martin SS, et al. *Prison J* 1999;79(3):294-320.
→ For more information, see http://www.cjdats.org/
→ For more information, see http://www.drugabuse.gov/Blending/
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**) (GPRA)

AIDS International Training and Research Program: The AIDS International Training and Research Program (AITRP) began in 1988 as one of the first of a new generation of research training programs sponsored by FIC. This program supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries (LMICs) to conduct multidisciplinary biomedical and behavioral research to address the AIDS epidemic in their countries. This program provides training for scientists from LMIC institutions to strengthen HIV-related research and public health capacities at their institutions. AITRP has trained more than 1,500 trainees. Importantly, several partnerships between AITRP programs and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) were developed in 2008 and 2009. The training provided under the AITRP program targets a cohort of scientists who benefit from the critical thinking and problem-solving skills received through research training. These skills move them forward in their careers

into leadership and policymaking positions in public health in their countries. Many PEPFAR programs are directed in-country by clinician/scientists who have received FIC-supported training. This training, therefore, is an important foundation for the long-term sustainability of the PEPFAR programs. There are many successful partnerships between PEPFAR country teams and FIC AITRP grantees in Zambia, Tanzania, and Cote d'Ivoire.

→ For more information, see http://www.fic.nih.gov/programs/training_grants/aitrp/
→ This example also appears in Chapter 3: *Research Training and Career Development*
→ (E) (**FIC**, NCI, NHLBI, NIAID, NICHD, NIDA, NIMH, OD)

Emerging Infectious Diseases and Biodefense (including seasonal and other influenzas)

Evolution of Infectious Diseases: The NIH Evolution of Infectious Diseases Program supports research on how pathogens and hosts evolve and influence each other's evolution, a critical component to understanding how new diseases emerge and spread. Research focuses on genetic changes in pathogens and hosts, evolution of immunity, the impact of vaccines and antimicrobial drugs, evolution of antimicrobial resistance, co-evolution of molecular and cellular dynamics, and the importance of environmental context. Among the diseases being studied are influenza, malaria, and dengue.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-130
→ (E) (**NIGMS**)

Rapid Research Response to Emerging Disease Threats: The sudden and unpredictable emergence of infectious diseases requires advance preparation to safeguard public health. Because the groundwork of basic research can be crucial when new health threats arise, NIH conducts and supports research to increase basic knowledge of infectious diseases, and advance development of effective diagnostics, therapeutics, and vaccines. In the case of severe acute respiratory syndrome (SARS), for instance, NIH's broad portfolio of basic research grants on coronaviruses was critical to understanding the new pathogen. NIH has developed new funding initiatives for accelerated, targeted research to encourage collaborative and product development-oriented projects. NIH also provides needed infrastructure and resources to support the research community in the event of a public health emergency. For example, the national network of Vaccine and Treatment Evaluation Units provides a ready means to conduct clinical trials to evaluate vaccines and treatments for outbreaks such as the novel 2009 H1N1 influenza. In 2009, NIH awarded new funding for 1 and renewed funding for 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs). The RCEs are a critical component of the U.S. research infrastructure for infectious diseases, and are designed to respond flexibly to changing scientific needs and priorities. RCE researchers are developing new or improved ways to treat, diagnose, or prevent illnesses, including anthrax, West Nile fever, plague, and dengue fever. The RCEs are prepared to provide scientific expertise to first responders in an infectious disease-related emergency, whether such an emergency arises naturally or through an act of bioterrorism.

→ For more information, see http://www3.niaid.nih.gov/LabsAndResources/resources/rce/default.htm
→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/RCEs_ARRA.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAID**) (ARRA)

2009 H1N1—Responding to Pandemic Influenza: NIH is engaged fully in the government-wide effort to understand the 2009 H1N1 virus and rapidly develop countermeasures. Activities are being conducted in NIH-supported research networks such as the Centers of Excellence in Influenza Research and Surveillance (CEIRS) and Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs), as well as by industry partners and individual NIH grantees. NIH used its longstanding vaccine clinical trials infrastructure—notably, the network of Vaccine and Treatment Evaluation Units—to quickly evaluate pilot lots of vaccine candidates for safety and ability to induce protective immune

responses, and to determine the appropriate dose and number of dosages. Because of increased resistance to existing antiviral therapeutics, NIH is working to develop the next generation of influenza therapeutics/antivirals. Three drugs now in clinical testing include a long-acting neuraminidase inhibitor, an inhibitor of the enzyme that replicates viral genes, and a drug that prevents the virus from entering human lung cells. NIH will evaluate how well these candidate antiviral drugs block the 2009 H1N1 strain and will screen other compounds for activity against the virus. NIH also is developing diagnostic platforms that can rapidly identify a wide variety of pathogens in clinical samples, including specific subtypes of influenza. NIH is accelerating development of these platforms to provide improved diagnostics for 2009 H1N1 influenza. In addition, enrollment is complete for an NIH pandemic influenza H1N1 DNA vaccine Phase I clinical trial that has begun, and NIH scientists are conducting basic research to develop universal influenza vaccines that can protect against multiple influenza strains.

→ For more information, see http://www3.niaid.nih.gov/topics/Flu/understandingFlu/2009h1n1.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAID**)

Centers of Excellence for Influenza Research and Surveillance: NIH established the Centers of Excellence for Influenza Research and Surveillance (CEIRS) program in March 2007 to continue and expand its animal influenza surveillance program internationally and domestically, and to focus on several high-priority areas in influenza research. The program provides the government with information and public health tools and strategies to control and lessen the impact of epidemic influenza and the increasing threat of pandemic influenza. CEIRS activities lay the groundwork for the development of new and improved control measures for emerging and reemerging influenza viruses. Such measures include determining the prevalence of avian influenza viruses in animals in close contact with humans; understanding how influenza viruses evolve, adapt, and transmit; and identifying immunological factors that determine disease outcome. Each CEIRS site focuses on either (1) animal influenza surveillance for the rapid detection and characterization of influenza viruses with pandemic potential, or (2) pathogenesis and host response research to enhance understanding of the molecular, ecological, and/or environmental factors that influence pathogenesis, transmission, and evolution of influenza viruses; and to characterize the protective immune response. Currently, the CEIRS are responding to the 2009 H1N1 influenza outbreak by conducting research on pathogenicity and transmission of H1N1 and studying immune response to this novel influenza strain.

→ For more information, see http://www3.niaid.nih.gov/topics/Flu/default.htm
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIAID**)

Influenza Virus Resources: NIH maintains the Influenza Virus Resource, a database of influenza virus sequences that enables researchers around the world to compare different virus strains, identify genetic factors that determine the virulence of virus strains, and look for new therapeutic, diagnostic, and vaccine targets. The resource was developed using publicly accessible data from laboratories worldwide in addition to targeted sequencing programs such as NIH's Influenza Genome Sequencing Project. Updated daily, this comprehensive sequence resource includes more than 90,000 influenza sequences and more than 2,000 complete genomes. In the spring of 2009, with the rapid emergence of the 2009 H1N1 pandemic, the database received more than 2,200 influenza sequences from publicly accessible databases and included sequences from CDC and labs from 35 countries. By the end of 2009, nearly 10,000 H1N1 sequences were in the database. The combination of extensive sequence data and advanced analytic tools provided researchers worldwide immediate access for investigating the rapid spread of this flu and developing vaccines for combating it. Other influenza virus information resources also were developed in response to 2009 H1N1. To facilitate access to the scientific literature, a pre-formulated search for 2009 H1N1 papers was added to PubMed. A 2009 H1N1 Flu page with comprehensive information on Federal response, international resources, transmission, prevention, treatment, genetic makeup, and veterinary resources was added to Enviro-Health Links, which provides links to toxicology and environmental health

topics of recent special interest, including information in Spanish. For the general public, patients, family members, and caregivers, a health topic on 2009 H1N1 flu, in Spanish and English, was added to the MedlinePlus consumer health resource.

→ Bao Y, et al. *J Virol* 2008;82(2):596-601. PMID: 17942553. PMCID: PMC2224563.
→ For more information, see http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html
→ For more information, see http://www.pubmed.gov
→ For more information, see http://sis.nlm.nih.gov/enviro/swineflu.html
→ For more information, see http://www.nlm.nih.gov/medlineplus/h1n1fluswineflu.html
→ For more information, see http://www.nlm.nih.gov/medlineplus/spanish/h1n1fluswineflu.html
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**NLM**)

Developing Biodefense Vaccines and Therapeutics: NIH is the lead Federal agency within HHS for conducting and supporting research on potential agents of bioterrorism and emerging infectious diseases that directly affect human health. NIAID is the lead Institute within NIH in this area. Counter measures against NIAID Category A-C priority pathogens, microbes, and toxins, which are considered to be the most significant threats to the Nation's well-being, are either nonexistent, of limited utility, or threatened by the emergence of antimicrobial resistance or intentional engineering to increase virulence or decrease drug susceptibility. Given the absence of a substantial commercial market, regulatory hurdles, and extensive clinical trial requirements, the private sector has little incentive to invest in countermeasures. To remedy this situation, NIH supports unique partnerships among government, industry, small businesses, and academia to facilitate the movement of promising products through all stages of the drug research and development pipeline, with the goal of developing vaccines and therapeutics against diseases such as smallpox and botulism, as well as for infections with Ebola, Marburg, and West Nile virus infection. NIH advances include progress toward vaccines and/or therapeutics for anthrax, smallpox, and West Nile viruses. NIH supported development of a nonhuman primate model for plague; studies in the model have been completed for three licensed antibiotics for plague. In addition, advanced development and production continues for a recombinant protective antigen vaccine for anthrax and a modified vaccinia Ankara vaccine for smallpox.

→ For more information, see http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAID**)

Developing New Adjuvants to Boost Vaccine Effectiveness: Adjuvants activate the body's innate immune system, a prerequisite for effective responses by the adaptive immune system—antibody-producing B cells and antigen-specific T cells. In 2004, NIH launched the “Innate Immune Receptors and Adjuvant Discovery” initiative in response to the growing need to boost the effectiveness of vaccines against potential agents of bioterrorism and emerging infectious diseases. The initiative encouraged the discovery of novel adjuvants that stimulate the innate immune response through proteins known as pattern recognition receptors, which the innate immune system uses to identify microbial pathogens. To build on the success of this program, NIH initiated the Adjuvant Development program in 2008. Four groups were funded to advance identified adjuvants toward licensure for human use in vaccines against diseases such as influenza and tuberculosis, as well as infection with West Nile virus. The “Innate Immune Receptors and Adjuvant Discovery” initiative was reissued—inviting new grant applications—in FY 2009 to continue the generation of potential adjuvant candidates. The research focus on adjuvants yielded a major science advance in 2008 when several groups of NIH-supported investigators discovered that alum activates the innate immune system by stimulating clusters of proteins called inflammasomes, found inside certain cells. This new information should provide keys to better understanding adjuvant function and should facilitate the design of new vaccine adjuvants.

→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2008/alum_vaccine.htm
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIAID**)

Confronting the Challenge of Antimicrobial Resistance: Antimicrobial resistance has become a major public health threat that is severely jeopardizing the utility of many "first-line" antimicrobial agents. The development of resistance can be caused by many factors, including the inappropriate use of antibiotics. NIH supports a robust basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes. NIH also is pursuing translational and clinical research in this area, including clinical studies to test interventions for community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection and to evaluate the efficacy of off-patent antimicrobial agents. NIH laboratories are at the forefront of understanding the fundamental causes of resistance—from studies of the disease-causing organisms and the progression of disease to research on the advantages and shortcomings of current antibiotics. Specific research foci of NIH researchers and NIH-supported grantees include MRSA and vancomycin-resistant *Staphylococcus aureus* (VRSA) (commonly acquired in community settings), and drug-resistant malaria and tuberculosis. NIH supports genomic sequencing through its Microbial Sequencing Centers; researchers at these centers have sequenced the genomes of numerous disease-causing bacteria, viruses, parasites, and fungi, which may help identify mechanisms of resistance and when and where resistance emerges.

→ For more information, see http://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm
→ This example also appears in Chapter 3: *Genomics* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAID**) (GPRA)

NIH Countermeasures Against Chemical Threats (CounterACT) Research Program: The CounterACT Research Network, as reflected in an NIH GPRA goal, develops medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The Network, which has collaborated with the U.S. Department of Defense (DOD) from its inception in 2006, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. One promising countermeasure, midazolam, which DOD researchers identified as a potential countermeasure against chemical agent-induced seizures, has entered clinical trials through the NIH Neurological Emergency Clinical Trials Network, and NIH is collaborating with DOD to complete animal studies necessary for its FDA approval as a nerve agent treatment. The New Drug Application is expected early FY 2010, with approval anticipated by the end of the year. The network also has developed six other lead compounds as therapeutics for cyanide, nerve agent, chlorine, and sulfur mustard, and has participated in pre-Investigational New Drug application meetings with FDA related to these efforts. One of the diagnostic devices developed by the program is being used in an NIH clinical trial. Three chemical agent therapeutics developed by the program also show promise as therapies for radiation exposures, and the program is collaborating with the NIH Medical Countermeasures Against Radiological and Nuclear Threats program.

→ For more information, see http://www.ninds.nih.gov/research/counterterrorism/counterACT_home.htm
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00809146
→ For more information, see http://nett.umich.edu/nett/welcome
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NINDS**, NEI, NIAID, NIAMS, NICHD, NIEHS, NIGMS) (GPRA)

Medical Countermeasures Against Nuclear and Radiological Threats: NIH continues to lead the HHS effort to sponsor and coordinate research to develop medical countermeasures to mitigate and/or treat radiation-induced damage. Many candidate medical countermeasures are in the early stages of discovery; however, substantial effort focuses on later

development as lead compounds are identified. Animal model testing is underway for 59 medical countermeasures for hematopoietic (HE) acute radiation syndrome (ARS), 18 for gastrointestinal (GI) ARS, 13 for radiation-induced lung pneumonitis and/or fibrosis, 13 for kidney injury, 7 for brain injury, and 17 for skin, including combined injuries (radiation plus burns or wounds). Three orally bioavailable forms of diethylenetriaminepentaacetic acid (DTPA), which may be used to treat victims with internal radionuclide contamination from fallout or "dirty bombs," are in development. Research into 6 lead, orally bioavailable compounds with enhanced properties for removing radioactive isotopes from the body also is ongoing. Interactions with 87 biotechnology companies through an advanced development contract have led to the identification and initial animal efficacy confirmation for 7 HE-ARS candidate medical countermeasures and 2 GI-ARS candidate medical countermeasures. Other areas of research include characterization of genomic, proteomic, metabolomic and cytogenetic markers of radiation injury, and development of biodosimetry devices to provide accurate and timely radiation exposure information to assist in medical triage and treatment strategies.

→ For more information, see http://www3.niaid.nih.gov/topics/radnuc/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAID**) (ARRA)

Infrastructure and Research Resources

Translational Research at Primate Research Centers: Nonhuman primates are critical components for translational research because of their close physiological similarities to humans. Nonhuman primates widely are used for both hypothesis-based and applied research directly related to human health, such as the development and testing of vaccines and therapies. The NIH-supported National Primate Research Centers (NPRCs) and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using nonhuman primates. NIH support for the centers ensures that these specialized resources are available to the research community. Several NIH ICs provide funding to investigators for specific research projects that use NPRC resources, thus increasing the efficiency of projects involving use of nonhuman primates. For example, in FY 2008, more than 1,000 research projects and more than 2,000 investigators used the animals and other resources provided by the NPRCs. Highlights of research activities include:

- Use of the simian immunodeficiency virus for AIDS-related research, including development and testing of novel microbicides to prevent infection by HIV, the virus that causes AIDS, and testing of AIDS vaccine candidates.
- Identification of the central role of specific genes and molecules in drug addiction and neurological conditions and diseases, studies of the biochemistry and physiology of drug and alcohol addiction, and development of stem cell-based therapies for neurodegenerative diseases.
- Development of the first nonhuman primate model of a neurodegenerative disease-Huntington's disease.

→ Yang SH, et al. *Nature* 2008;452(7197):921-4. PMID: 18488016. PMCID: PMC2652570.
→ For more information, see http://www.ncrr.nih.gov/comparative_medicine/resource_directory/primates.asp
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**, NIA, NINDS)

Chemical Genomics: The NIH Chemical Genomics Center (NCGC), part of the NIH Roadmap for Medical Research, is an ultra high-throughput, small molecule screening center with pharmaceutical-scale power that provides state-of-the-art technologies to researchers across the United States. The center provides the translational infrastructure needed for potential drug discoveries, particularly for drugs aimed at diseases often overlooked by the private sector. For instance, schistosomiasis, also known asbilharzia or snail fever, affects an estimated 207 million people in more than 70 developing nations in tropical areas. Recently, NCGC, collaborating with NIH-funded university researchers, discovered that chemical compounds known as oxadiazoles can inhibit an enzyme vital to survival of the parasite that causes schistosomiasis. NCGC also will be a vital collaborator in a new congressionally mandated program, called Therapeutics for Rare and

Neglected Diseases, which aims to encourage and speed the development of new drugs for conditions that are of relatively little interest to the pharmaceutical industry. In addition, in partnership with NIH's National Toxicology Program and the Environmental Protection Agency, NCGC is using its high-speed robotic system to screen chemicals for toxicity in cells and isolated molecular targets. This effort, known informally as the Tox21 Collaboration (for Toxicology in the 21st Century), has the potential to make crucial discoveries that will protect the public by identifying and understanding chemical toxicants to which millions of people are exposed on a regular basis, from pesticides to common household cleaners.

→ Sayed AA, et al. Nat Med 2008;14(4):407-12. PMID: 18345010. PMCID: PMC2700043.
→ For more information, see http://nihroadmap.nih.gov/hmp/index.asp
→ For more information, see http://ncgc.nih.gov/index.html
→ For more information, see http://rarediseases.info.nih.gov/TRND/
→ For more information, see http://www.genome.gov/26524878
→ (I) (**NHGRI, NIMH**, Common Fund - all ICs participate, NIAID, NIEHS) (GPRA)

Specialized Centers of Research (SCORs) on Sex and Gender Factors: The SCORs on Sex and Gender Factors Affecting Women's Health provide an innovative and interdisciplinary approach to advancing research on the influence of sex and gender as it relates to health and disease. Each of these SCORs emphasizes research in an area of clinical importance to women's health. The 11 current SCORs, co-funded with 5 NIH ICs and the Food and Drug Administration, address sex/gender research in the areas of depression, pain, urinary tract infection, reproductive issues, substance abuse, and osteoporosis. An example of scientific advances includes the isolation of an estrogen receptor alpha signaling process that therapeutically could be downregulated to reduce the risk for obesity and type 2 diabetes in menopausal women. In 2009, the SCORs contributed 116 journal articles, 176 abstracts, and 63 other publications (reviews and book chapters) resulting from their research.

→ For more information, see http://orwh.od.nih.gov/interdisciplinary/SCORs.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**ORWH**, FDA, NIAMS, NICHD, NIDA, NIDDK, NIMH)

New Approaches in Diagnostic Microbiology: The basic research tools developed by NIH to map the human genome form the foundation for new approaches to detect and identify infectious organisms. These techniques for sequencing the genomes of bacteria and fungi are faster and more precise than the biochemical and microscopic techniques that have been used historically in clinical laboratories to identify organisms responsible for community- and hospital-acquired infections. Additionally, collaborative work between the NIH Proteomic Research Centers and commercial companies led to the development of a complementary, novel approach for organism identification. A database of protein profiles, generated using the technique of mass spectrometry, was developed that uniquely characterizes individual species of bacteria and fungi. At NIH these genomic and proteomic techniques led to the discovery of previously unknown organisms (e.g., *Granulibacter bethesdensis*, responsible for infections in chronic granulomatous disease patients; and a currently unnamed bacterium responsible for pneumonia in a lymphoma patient), the rapid detection of *Mycobacterium tuberculosis* and other pathogens directly in clinical specimens, and the routine identification of virtually all bacteria and fungi isolated in clinical laboratories. With the development of these techniques and proof of their value, it is anticipated that other clinical microbiology laboratories will be able to adopt them for routine use.

→ (I) (**CC**, NHGRI, NIAID)

International Epidemiologic Databases to Evaluate AIDS (IeDEA): The goal of the IeDEA program is to conduct analyses based on comparable data from multiple regions and studies. This initiative has established international regional centers for the collection and harmonization of data and has created an international research consortium to address unique

and evolving research questions in HIV/AIDS currently unanswerable by single cohorts. High-quality data are being collected by researchers throughout the world. This initiative provides a means to establish and implement methodology to pool the collected data effectively—thus providing a cost-effective means of generating large data sets to address the high-priority research questions. Combination of data collected under various protocols frequently is very difficult and not as efficient as the collection of predetermined and standardized data elements. By developing a proactive mechanism for the collection of key variables, this initiative will enhance the quality cost effectiveness and speed of HIV/AIDS research. Participating regions include Canada and the United States, the Caribbean and Central and South America, Asia and Australia (excluding China), West Africa, Central Africa, East Africa, and Southern Africa.

→ For more information, see http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E) (**NIAID**, NCI, NICHD)

Adolescent Medicine Trials Network for HIV/AIDS (ATN): Although one-third to one-half of new HIV infections occur among adolescents and young adults, researchers know little about how the complex physiological changes associated with adolescence affect the transmission and course of HIV infection. NIH is supporting a national clinical research network to address the unique challenges and clinical management needs of HIV-positive adolescents and those at risk of infection. Researchers in this network are conducting biomedical, behavioral, and community-based studies to ensure that teens can benefit from the most promising preventive and treatment interventions. For example, one recently published study conducted by the ATN documented that HIV-positive adolescents frequently do not follow prescribed treatment regimens, and the study also identified several factors associated with nonadherence to therapy.

→ Rudy BJ, et al. *AIDS Patient Care STDS* 2009;(3):185-94. PMID: 19866536.
→ For more information, see http://www.atnonline.org
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NICHD**, NIDA, NIMH)

Biodefense Research Infrastructure: NIH has invested substantially in the intellectual and physical infrastructure needed to build the Nation's capacity for research on biodefense and emerging infectious diseases. This effort draws scientists from many disciplines to conduct research and development activities and to train future researchers. It also provides facilities that will greatly enhance the safe and efficient conduct of research on infectious agents. The NIH-funded infrastructure includes: (1) 11 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, which use a multidisciplinary approach to research and development, (2) 2 National Biocontainment Laboratories (with BSL-4 capacity, the highest level of containment), (3) 13 Regional Biocontainment Laboratories with BSL-3 capacity, and (4) services for researchers including performing medicinal and analytical chemistry, custom drug synthesis, formulation, clinical manufacturing, microbiology and virology screening, pharmacokinetics, and safety testing.

→ For more information, see http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/PublicMedia/BioLabs.htm
→ (E/I) (**NIAID**)

International Collaboration

The Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development: An estimated 20 million children under 5 are severely malnourished, leaving them more vulnerable to illness and early death, according to the World Health Organization. Poor nutrition in early childhood may lead to cognitive defects and poor physical development, may increase susceptibility to and severity of infections, and may diminish the effectiveness of childhood vaccines. Focusing on the interactions between communicable and noncommunicable conditions, in 2009, the Foundation for the National Institutes of Health, together with NIH, launched a 5-year study to investigate the links between malnutrition and intestinal infections and their effects on children in the developing world. With the

establishment of this remarkable public-private partnership, the project aims to shed light on critical questions related to the interaction between infections and growth and development. This large-scale, Gates-funded, NIH-led, $30 million project will support collaborative, multisite studies of malnutrition and enteric infections involving sites in Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa, and Tanzania. In addition to making critical discoveries that will help save the lives of the world's youngest and poorest children, the main objective of this research network is to create a standardized set of epidemiological tools to accurately study the links between intestinal infections and gut physiology as risk factors for malnutrition across a number of diverse sites in the developing world. This research effort will be conducted in collaboration with universities in the United States and institutions in the developing world.

→ For more information, see http://origem.info/malnutritionstudy/
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (O) (**FIC**, FNIH)

The Multinational Influenza Seasonal Mortality Study (MISMS): The MISMS project is an international collaborative effort to analyze national and global mortality patterns associated with influenza virus circulation. MISMS aims to describe synchrony in seasonal variations of various causes of mortality associated with influenza—by state, country, and region; to describe long-term temporal trends and interannual variations in influenza mortality patterns, both within and among countries, and their association with changes in circulating subtypes of influenza virus, antigenic characteristics, population factors, and vaccine coverage; to explore the seasonal patterns and burden of influenza mortality in tropical countries; and to understand the global circulation of influenza viruses. The project highlights NIH efforts at high-level coordination within HHS and has produced numerous publications that have had important implications for global policies and approaches to influenza, most notably a June 2009, *New England Journal of Medicine* article: “The signature features of influenza pandemics—Implications for policy.”

→ Miller MA, et al. *N Engl J Med* 2009;360(25):2595-8. PMID: 19423872.
Nelson MI, et al. *Virology* 2009;388(2):270-8. PMID: 19394063. PMCID: PMC2705899.
de Mello WA, et al. *PLoS One* 2009;4(4):e5095. PMID: 19352506. PMCID: PMC2663029.
Cattili G, et al. *PLoS One* 2009;4(3):e4842. PMID: 19290041. PMCID: PMC2653644.
Lipsitch M, Viboud C. *Proc Natl Acad Sci U S A* 2009;106(10):3645-6. PMID: 19276125. PMCID: PMC2656132.
Richard SA, et al. *Epidemiol Infect* 2009;137(8):1062-72. PMID: 19215637. PMCID: PMC2704924.
Barry JM, et al. *J Infect Dis* 2008;198(10):1427-34. PMID: 18808337.
Viboud C, Miller M. *PLoS Med* 2008;5(10):e216. PMID: 18959475. PMCID: PMC2573918.
Nelson MI, et al. *PLoS Pathog* 2008;4(8):e1000133. PMID: 18725925. PMCID: PMC2495036.
Miller MA, et al. *J Infect Dis* 2008;198(3):305-11. PMID: 18558871.
→ For more information, see http://origem.info/misms/index.php
→ (O) (**FIC**)

2009 Institute of Medicine Report, The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors: The recently released IOM report, *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*, reviews U.S. interest and investment in global health. This report is particularly timely and useful given the major changes in global health that have occurred since the last IOM report, *America's Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests*, was released in 1997. These changes include unprecedented interest and large fiscal commitments to global health by the U.S. government and nongovernmental sectors. The IOM leveraged the contributions of 18 NIH ICs to undertake this update with additional financial support from several key private and public entities. The study makes the case for why U.S. agencies and private sector entities should invest more heavily in global health. The report has five key recommendations that can inform NIH investments in global health in the coming years:

- Scale up existing interventions to achieve significant health gains
- Generate and share knowledge to address health problems endemic to the global poor

- Invest in people, institutions, and capacity-building with global partners
- Increase U.S. financial commitments to global health
- Set the example of engaging in respectful partnerships

The IOM panel was chaired by Dr. Harold Varmus and Ambassador Thomas Pickering. A preliminary report, titled *The U.S. Commitment to Global Health: Recommendations for the New Administration*, was released in December 2008. In May 2009, the final report, titled *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*, was released.

→ For more information, see http://www.iom.edu/Reports/2009/The-US-Commitment-to-Global-Health-Recommendations-for-the-Public-and-Private-Sectors.aspx
→ For more information, see http://www.iom.edu/Reports/2008/The-US-Commitment-to-Global-Health-Recommendations-for-the-New-Administration.aspx
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (O) (**FIC**, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS)

Inflammation, Immunology, and Cancer Virology: Several NIH programs are working to facilitate and rapidly translate advances in the discovery, development, and delivery of immunologic and antiviral approaches to improve the prevention and treatment of cancer, cancer-related viral diseases, and AIDS-associated malignancies. One notable example with implications for therapeutic cancer vaccine development is the discovery that co-delivery of Interleukin (IL)-15 with vaccines results in a more robust immune response both at the time of vaccine administration and in the event that the target antigen is encountered a second time. (IL-15 is a protein that regulates activation and proliferationn of some cells in the immune system.) IL-15 currently is in production for large-scale clinical trials. The human papillomavirus (HPV) Vaccine Trial in Costa Rica is a multiyear effort designed to test the ability of virus-like particle vaccines, originally developed at NIH, to protect against HPV16/18 infection. In addition to evaluating vaccine efficacy, the trial is examining broader measures of vaccine impact as well as immunity, natural history of HPV, and cervical neoplasia.

→ Oh S, et al. *Proc Natl Acad Sci U S A* 2008;105(13):5201-6. PMID: 18362335. PMCID: PMC2278231.
→ For more information, see http://ccr.nci.nih.gov
→ For more information, see http://home.ccr.cacner.gov/coe/immunology/
→ For more information, see https://ccrod.cancer.gov/confluence/display/CEHCV/Home
→ This example also appears in Chapter 2: *Cancer*
→ (E/I) (**NCI**, NIAID, OAR, ORWH)

New Insights into a Blinding Disease Prevalent in Developing World: Trachoma is a leading cause of blindness in the developing world and affects an estimated 8 million people. The disease is caused by *Chlamydia trachomatis*, a microorganism that is transmitted by flies and spreads from person to person through contact with eye discharge from infected persons. Repeated infections scar the eyelid and cause eye lashes to scrape and irreversibly damage the transparent cornea. Trachoma occurs in overcrowded areas of extreme poverty that lack clean water and sanitation. Due to poor hygiene, specifically dirty faces, children are most likely to exchange eye discharge, making them more susceptible to trachoma. There has been considerable success in reducing trachoma in areas with moderate infection rates using the oral antibiotic azithromycin. However, in severely affected communities, infection returns rapidly after treatment. NIH-supported investigators conducted a clinical trial assessing the benefit of a longer-term, 4-course antibiotic treatment administered over 18 months to children in rural Ethiopia. Trachoma prevalence was 64 percent before treatment and dropped to less than 3 percent after treating for 6 months. However, 18 months after treatment was completed, infection rate returned to 25 percent. This study suggests that eradication must include sustainable programs that emphasize sanitation and personal hygiene and/or complete local elimination to stop the return of the disease in communities with very high prevalence.

→ Lakew T, et al. *PLoS Negl Trop Dis* 2009;3(2):e376. PMID: 19190781. PMCID: PMC2632737.
→ For more information, see http://www.plosntds.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0000376
→ (E) (**NEI**)

NIH Strategic Plans Pertaining to Infectious Diseases and Biodefense Research

National Institute of Allergy and Infectious Diseases (NIAID)

- *NIAID: Planning for the 21st Century — 2008 Update*
- *NIAID Research Agenda for Malaria (2008)*
- *NIAID Influenza Research: 2009 Progress Report*
- *The Research Agenda of the National Institute of Allergy and Infectious Diseases for Antimicrobial Resistance (2008)*
- *NIAID Strategic Plan for Biodefense Research (2007 update)*
- *Report of the Blue Ribbon Panel on Influenza Research (2006)*
- *NIAID Research Agenda Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis (2007)*
- *Development of Reagents for TLR and Other Innate Immune Receptors: Present Challenges — Future Directions (2007)*
- *Immunosuppression and Vaccination in Special Populations (2004)*

Special Populations

- *Women's Health in the U.S.: Research on Health Issues Affecting Women (2004)*

National Institute of Dental and Craniofacial Research (NIDCR)

- *NIDCR Strategic Plan*
- *NIDCR Implementation Plan*

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Branch Reports to Council with Future Scientific Directions

- *Pediatric, Adolescent, and Maternal AIDS Branch (PAMAB), NICHD, Report to the NACHHD Council, June 2007*

National Institute on Drug Abuse (NIDA)

- *Five-Year Strategic Plan 2009*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- *National Institute on Alcohol Abuse and Alcoholism Five-Year Strategic Plan, FY 08-13*

Recommendations of the NIAAA Extramural Advisory Board (EAB)

- *Developing an NIAAA Plan for HIV-Related Biomedical Research*

National Center for Complementary and Alternative Medicine (NCCAM)

- *Expanding Horizons of Health Care: Strategic Plan 2005-2009*

John E. Fogarty International Center (FIC)

- *Pathways to Global Health Research: Strategic Plan 2008-2012*

Office of AIDS Research (OAR)

- *FY 2008 Trans-NIH Plan for HIV-Related Research*
- *FY 2009 Trans-NIH Plan for HIV-Related Research*
- *FY 2010 Trans-NIH Plan for HIV-Related Research*

Other Trans-NIH Strategic Plans

- *NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats*
  NCI, NHLBI, NIAID, NIEHS
- *NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats*
  NEI, NHLBI, NIAID, NIAMS, NIEHS, NIGMS, NINDS

Interagency Plans

- *HHS Action Plan to Prevent Healthcare-Associated Infections*
- *A Public Health Action Plan to Combat Antimicrobial Resistance*
  http://www.cdc.gov/drugresistance/actionplan/update_08.htm

[28] For more information, see http://www3.niaid.nih.gov/topics/BiodefenseRelated/default.htm
[29] For more information, see WHO *Disease Control Priorities Project* Infectious Diseases chapter (April 2006), http://www.dcp2.org/file/6/DCPP-InfectiousDiseases.pdf.
[30] For more information on the global HIV/AIDS pandemic, see http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2009/2009epidemic_update.asp.
[31] For more information on tuberculosis, see http://www3.niaid.nih.gov/topics/tuberculosis.
[32] For more information, see http://www.who.int/entity/mediacentre/factsheets/fs310.pdf.
[33] For more information, see http://www.who.int/features/factfiles/malaria/en/index.html.
[34] For more information, see *Global Burden of Disease and Risk Factors*. Eds. Lopez AP, et al. Oxford University Press and the World Bank. 2006. Available at http://files.dcp2.org/pdf/GBD/GBDFM.pdf.
[35] For more information, see WHO *Disease Control Priorities Project*, Infectious Diseases chapter (April 2006), see http://www.dcp2.org/file/6/DCPP-InfectiousDiseases.pdf.
[36] For more information, see http://www.dcp2.org/main/Home.html.
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[44] For information about NIH funding for research on the lung microbiome, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-006.html.
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Autoimmune Diseases

Just a few decades ago, 30 percent of people died within 25 years after being diagnosed with type 1 diabetes, an autoimmune disease. One in 4 people developed kidney failure, and diabetic retinopathy was responsible for 12 percent of new cases of adult blindness. Now, the outlook for people with longstanding type 1 diabetes has greatly improved, largely due to long-term NIH-supported research.

The concept of controlling blood glucose tightly to prevent diabetes-related complications was untested. To address this gap in knowledge, in 1983, NIH launched the Diabetes Control and Complications Trial (DCCT), which enrolled 1,441 people with type 1 diabetes. In 1993, the trial showed that intensive control of blood glucose reduced the risk for eye, kidney, and nerve complications by a dramatic 50 percent to 75 percent. Upon completion of the original landmark study, intensive therapy rapidly became the standard of care nationwide.

Nearly all participants in the original trial continue to be followed in an ongoing successor study, the Epidemiology of Diabetes Intervention and Complications (EDIC). EDIC has found that participants show not only continued dramatic reductions in eye, kidney, and nerve complications, but also more than 50 percent reductions in heart disease and stroke. These landmark discoveries—along with advances in insulin formulations, insulin delivery, glucose monitoring, and the treatment of heart disease risk factors—now have translated into greatly improved health outcomes for people with type 1 diabetes. In 2009, DCCT/EDIC researchers reported that 30 years after their initial diagnosis, fewer than 1 percent of the intensively controlled participants have become blind, required kidney replacement, or had an amputation. These exciting findings reinforce the message that people with type 1 diabetes should begin intensive glucose control as soon as possible after diagnosis to greatly improve their long-term health.

Introduction

Autoimmune diseases are a group of more than 80 chronic, and often disabling, illnesses that develop when underlying defects in the immune system lead the body to attack its own organs, tissues, and cells. The causes of autoimmune diseases remain unknown, although genetic factors play major roles in susceptibility. Some of these diseases may be triggered by an infectious agent or an environmental exposure, especially in individuals who have inherited susceptibility.

Emerging data indicate that the incidence and prevalence of some autoimmune diseases, such as type 1 diabetes and celiac disease, are increasing. This trend has serious implications including the future physical, psychosocial, and financial toll of these illnesses. NIH recognizes that more needs to be done to close the gaps in knowledge and reduce the rising impact of autoimmune diseases. NIH is committed to advancing the understanding of how autoimmune diseases develop and to applying results of basic research to improve the health and quality of life of patients affected with these diseases.

Some of the more common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, multiple sclerosis, celiac disease, and inflammatory bowel disease. Organ-specific autoimmune diseases are characterized by immune-mediated injury localized to a single organ or tissue, for example, the pancreas in type 1 diabetes and the central nervous system in multiple sclerosis. In contrast, nonorgan-specific diseases, such as systemic lupus erythematosus (lupus), are characterized by immune reactions against many different organs and tissues, which may result in widespread injury.

Autoimmune diseases can affect any part of the body and have myriad clinical manifestations that can be difficult to diagnose. At the same time, autoimmune diseases share some features related to their onset and progression. In addition, overlapping genetic traits enhance susceptibility to many of these diseases, so that a patient may suffer from more than one autoimmune disorder, or multiple autoimmune diseases may occur in the same family. Furthermore, scientists suspect that hormones may play a role in the development of at least some autoimmune disorders. For these and other reasons,

autoimmune diseases are best recognized as a family of related disorders that must be studied together as well as individually.

Many autoimmune diseases disproportionately affect women, and this group of diseases is among the leading causes of death for young and middle-aged women.[79] Although treatments are available for numerous autoimmune diseases, cures have yet to be discovered and patients face a lifetime of illness and treatment. They often endure debilitating symptoms, loss of organ function, and hospitalization. The social and financial burden of these diseases is immense and includes poor quality of life, high health care costs, and substantial loss of productivity.

NIH supports research and promotes progress toward conquering autoimmune diseases through a wide range of research projects and programs. Because autoimmune diseases span many organ systems and clinical disciplines, multiple NIH Institutes conduct and support autoimmune disease research, often in collaboration with professional and patient advocacy organizations. The congressionally mandated Autoimmune Diseases Coordinating Committee (ADCC) facilitates trans-Institute collaboration and coordination in the development, review, award, and post-award monitoring of solicited autoimmune diseases research programs.

Several decades of intensive research have produced a wealth of information that has transformed conceptual understanding of autoimmune diseases. This research has helped set the stage for major advances in diagnosis, treatment interventions, and prevention. In particular, scientists are studying the causes of these diseases through epidemiologic and mechanistic studies, discovering the genetic and environmental factors that make people susceptible to autoimmune diseases, and conducting broad investigations into basic immunology. NIH supports research to translate knowledge about autoimmune diseases into broadly applicable prevention strategies that arrest the inflammatory and immune processes before they can irreversibly damage the body. Other research focuses on the development and testing of effective therapies and sensitive tools for early and definitive diagnosis, disease staging, and identification of at-risk individuals. NIH enhances this translational research through the conduct of training and education activities for researchers and clinicians in collaboration with nonprofit and advocacy organizations and through effective information dissemination to patients, their families, and the public.

A major goal of autoimmune disease research is to "re-educate" the immune system by using tolerance induction strategies that selectively block or prevent deleterious immune responses while leaving protective immunity intact.

A major goal of autoimmune disease research is to "re-educate" the immune system by using tolerance induction strategies that selectively block or prevent deleterious immune responses while leaving protective immunity intact. NIH-supported research integrates mechanistic studies of tolerance induction and suppression of disease into clinical research studies and conducts trials of a variety of agents and strategies through dedicated clinical networks.

Overarching priority areas that promise to accelerate autoimmune disease research include biomarker identification, bioinformatics, and application of new technologies. Biomarkers hold great promise for earlier and more accurate diagnosis of autoimmune diseases, better prediction of disease flare-ups, and improved monitoring of disease progression and response to treatment. New technologies, such as genome-wide association studies (GWAS), provide scientists with improved means to identify susceptibility genes and molecular pathways that may be targeted in the development of therapies. Other genomic and proteomic technologies make it possible to characterize antibodies in serum, which may provide vital insights into the mechanisms of onset and progression of autoimmune disease. Bioinformatics tools, which help scientists to assemble and analyze large amounts of data, will be particularly important. Many of these research areas intersect with initiatives planned under the NIH Roadmap, which fosters trans-NIH and multidisciplinary collaboration as a way to address complex challenges in biomedical research.

Burden of Illness and Related Health Statistics

Although many individual autoimmune diseases are rare, collectively they affect millions of Americans, and for unknown reasons, their incidence and prevalence are rising. Since cures are not yet available for most autoimmune diseases, patients face a lifetime of illness and treatment. They often endure debilitating symptoms, loss of organ function, reduced productivity at work, and high medical expenses. Some examples of current statistics on the incidence and prevalence of autoimmune diseases in the United States include:

- An estimated 1.3 million adults ages 18 and older (about 0.6 percent of the population) have rheumatoid arthritis and about 294,000 children have juvenile arthritis.[80]
- About 895,000 to 1.8 million people have type 1 diabetes. About 15,000 people younger than age 20 are diagnosed annually with type 1 diabetes.[81,82]
- In the general U.S. population, prevalence of multiple sclerosis is 0.9 per 1,000.[83]
- About 322,000 people have definite or probable lupus. Of this number, 161,000 people have received a definite diagnosis.[84]
- As many as 1.4 million people have inflammatory bowel disease.[85]
- More than 2 million Americans have celiac disease.[86]

NIH Funding for Autoimmune Disease Research

Actual NIH funding support levels for autoimmune diseases research were $762 million in FY 2008, and $879 million and $138 million in FY 2009, respectively, for non-ARRA (regular appropriations) and ARRA (Recovery Act appropriations). Click on the funding levels, which are live links, to produce detailed project listings. These lists are derived from the NIH Research, Condition, and Disease Categorization (RCDC) system. In addition, the table at the end of this chapter indicates some of the research areas involved in this investment (see *Estimates of Funding for Various Research, Condition, and Disease Categories*).

Summary of NIH Activities

NIH seeks to understand the onset and progression of autoimmune diseases and to use that knowledge to develop better strategies for disease prevention, diagnosis, and treatment. With more than 80 distinct autoimmune diseases, this may seem to be a daunting task. However, the many commonalities in the mechanisms that cause autoimmune disorders mean that research on one autoimmune disease often advances our understanding of others.

Providing Research Resources and Infrastructure

Many autoimmune diseases are rare, and researchers often must engage in national and international collaborative research to ensure access to sufficient numbers of patients and tissue samples to conduct their studies. NIH provides resources to facilitate this collaboration. For example, NIH supports patient registries for numerous autoimmune diseases, including alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, epidermolysis bullosa acquisita, juvenile and adult rheumatoid arthritis, systemic lupus erythematosus (lupus), pediatric lupus, psoriasis, Sjogren's syndrome, and scleroderma. Some disease registries also contain relevant clinical data linked to tissue samples.

Disease registries provide an important epidemiological resource for tracing the natural history of an autoimmune disease, assessing its burden in different populations, and identifying and tracking trends in incidence and prevalence. NIH-supported disease registries, as well as biological sample repositories, also have been instrumental in the successful application of genome-wide association studies (GWAS) to the study of autoimmune diseases (see *Understanding the Genetics of Autoimmune Diseases* in this section for more details).

NIH-supported research resources also include programs for the preclinical development of therapeutic agents; biological specimen repositories; animal models; antibodies and other research reagents; national data systems; provision of genetic, genomic, proteomic, high-throughput, and other emerging technologies and assays for specific projects; and research training programs. NIH supports infrastructure for clinical trials and preclinical, transdisciplinary, and translational research. Many of these resources and infrastructure elements are mentioned in more detail throughout this section.

Understanding the Genetic, Environmental, and Immunologic Factors Contributing to Autoimmune Disease

Genetic Factors

NIH-supported scientists are identifying the genetic underpinnings of autoimmune diseases. Their findings may elucidate molecular pathways of disease and identify possible therapeutic targets. GWAS are bringing new insights to this research by comparing the genomes of groups of people with an illness to groups of people who do not have the illness. This comparison improves the identification of even subtle genetic differences between affected and unaffected people. GWAS have yielded important information about disease risk, molecular pathways of disease development, and potential therapeutic targets in several autoimmune diseases, such as type 1 diabetes, multiple sclerosis, inflammatory bowel disease, psoriasis, rheumatoid arthritis, lupus, and ankylosing spondylitis. NIH supports follow-up studies to evaluate the likelihood that a person with a newly discovered genetic variation associated with disease susceptibility will develop the disease. Integration of GWAS, environmental, demographic, and other genetic data will yield a better understanding of the mechanisms leading to disease and the development of tools for disease prevention and treatment.

Genome-wide Association Studies have yielded important information about disease risk, molecular pathways of disease development, and potential therapeutic targets in several autoimmune diseases, such as type 1 diabetes, multiple sclerosis, inflammatory bowel disease, psoriasis, rheumatoid arthritis, lupus, and ankylosing spondylitis.

Lupus research advanced appreciably in FY 2008 and FY 2009 thanks to the study of the genetics of autoimmune diseases. NIH-supported investigators identified genetic variations in lupus patients that may lead to a prognostic test to detect disease flare-ups or transient increases in disease severity. Furthermore, the discovery of some genetic factors on the X chromosome yields an important clue to the preponderance of this disease in females.[87]

Environmental Factors

Research suggests that infectious agents, dietary factors, toxic agents, or psychosocial factors, such as stress, may contribute to the development of autoimmune diseases. However, the sometimes long delay between environmental exposure and the onset of clinical disease, as well as the interaction of multiple genes or environmental factors, makes it difficult to determine which environmental factors are important to disease development.

NIH supports research to determine how environmental exposures influence the development of autoimmune diseases. For example, The Environmental Determinants of Diabetes in the Young (TEDDY) is a large-scale study focused on pinpointing environmental factors that can trigger type 1 diabetes in genetically susceptible individuals. This international consortium follows individuals from birth until age 15 to identify factors that lead some but not all genetically predisposed children to develop the disease. Because type 1 diabetes and celiac disease share many risk genes, TEDDY investigators also are examining environmental triggers of celiac disease. The dataset and biologic samples amassed in TEDDY will provide a valuable resource for future studies. NIH-supported researchers also are studying environmental risk factors for multiple sclerosis to identify environmental triggers in patients known to have genetic susceptibility to the disease. The study of environmental triggers in a clinically and ethnically homogeneous study sample from the same geographic region (Wisconsin) will help identify these triggers—an important step toward disease control and prevention.

NIH-supported animal model research and other basic research efforts are helping to decipher the role of various environmental exposures in the development of autoimmunity. For example, investigators are using mouse models to study how mercury affects the onset and progression of systemic autoimmunity, autoimmune heart disease, neuropsychiatric lupus, and the neuroimmune system.

Immunologic Factors

NIH sponsors research to illuminate the causes of autoimmune diseases and the regulatory mechanisms that control autoantibody production and function. For example, researchers are studying the possible involvement of various types of immune cells, such as T cells, B cells, and "natural killer cells," in autoimmune diseases. In one study, investigators recently reported that individuals with lupus who have high levels of the protein CD19 in their B cells appear to have poorer clinical outcomes than lupus patients not displaying high levels of CD19.[88] Other research has shed light on the role of one type of T cell, T-helper cells, in autoimmune disease. Studies indicate that altered levels of IL-17, a protein that stimulates a particular subset of T-helper cells to release molecules that cause inflammation, are associated with the development of two autoimmune diseases: psoriasis and Job's syndrome.[89] Studies of this nature extend understanding of how autoimmune diseases develop and will enhance efforts to identify effective therapies. In another area of research, investigators are attempting to learn whether regions called "lipid rafts," which are found in the membranes of cells, may play a role in the development of autoimmune diseases.[90]

NIH supports a range of initiatives to better understand the mechanisms of autoimmune disease onset and progression and to develop effective interventions. The Somatic Hypermutation Group is using mouse models to study the onset and progression of lupus. One project is examining the possible role of a protein called "activation-induced deaminase" (AID), which triggers a process called somatic hypermutation. This process generates more specific antibodies to a wide variety of infectious agents or, in the case of autoimmunity, self proteins. The investigators found that decreased levels of AID resulted in a dramatic drop in the levels of a type of antibody associated with lupus and led to a decrease in the severity of lupus-induced inflammation of the kidney.[91]

The Cooperative Study Group for Autoimmune Disease Prevention (CSGADP), established in 2001, is a collaborative network of investigators seeking to understand how immune system dysfunctions may contribute to the development of autoimmune diseases, especially type 1 diabetes. Investigators at the six participating centers work to create and validate models of disease pathogenesis and therapy, use these models as validation platforms to test new tools for human studies, and encourage core expertise and collaborative projects for rapid translation from animal to human studies. Investigators recently reported that the development and progression of type 1 diabetes in mice may be characterized by differences in the expression of specific genes. Researchers also discovered specific patterns of gene expression that may prove useful as biomarkers of disease onset or progression.[92]

The NIH Centers of Research Translation (CORTs) are designed to bring together basic and clinical researchers to translate basic discoveries into new drugs, treatments, and diagnostics. Each center encompasses at least three projects, including one clinical and one basic research study. Several CORTs are investigating autoimmune diseases:

- The Center for Lupus Research investigates the role of different cell types in the origin and development of lupus, markers of disease activity and severity, and new targets for treatment.
- The Center for Genetic Dissection of Systemic Lupus Erythematosus studies mouse models of lupus to identify the genetic background of developmental stages of the disease. The research is based on previous studies that identified two major steps leading to lupus in mice, and aims to identify similar stages in the development of lupus in humans. The work also may uncover early markers and key molecular mediators of the disease, which could pave the way for new treatment opportunities.
- The Center for Research Translation in Scleroderma is studying the molecular basis of scleroderma to understand its underlying causes.

Clinical studies supported by the Environmental Autoimmunity Group (EAG) seek to understand the mechanisms for the development of autoimmune disease and reduce the burden of illness. The EAG focuses on the roles of genetic and environmental risk factors in the development of rheumatoid arthritis, lupus, systemic sclerosis (scleroderma), and idiopathic inflammatory myopathies. EAG studies include epidemiologic surveys, molecular genetic studies, and clinical investigations in disease pathogenesis, as well as the development of clinical tools for assessment of innovative therapies.

The Center for Human Immunology, Autoimmunity, and Inflammation is a new trans-NIH intramural initiative designed to study the human immune system. The center organizes integrated teams of physicians and basic scientists to perform research on immune pathophysiologies, the role of inflammation in a wide variety of common disorders, and the translation of new knowledge into improvements in disease diagnosis and treatment.

Improving the Diagnosis and Prognosis of Autoimmune Diseases

Autoimmune diseases can affect any part of the body and have myriad clinical manifestations that can be difficult to diagnose. Research on biomarkers—clinical signs that correlate with the onset or progression of disease—may lead to better techniques for diagnosing autoimmune disorders. Improvements in technologies that enable clinicians to more quickly identify and test biomarkers hold great promise for earlier and more accurate autoimmune disease diagnosis, better prediction of disease flares, and improved monitoring of disease progression and response to treatment.

Recent progress in identifying biomarkers for lupus provides an example of NIH's work in this area. Researchers have uncovered numerous genes involved in the expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene is associated specifically with severe forms of lupus that include kidney disease, but not skin manifestations. Researchers also have developed tests, based on gene expression analysis of blood samples, to predict episodes of lupus activity and guide individualized treatment.

NIH-supported researchers also have identified two biomarkers detectable through blood tests that can predict the occurrence of a flare of lupus disease activity. They also showed that moderate doses of prednisone can prevent flares in people who have these biomarkers.[93]

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Developing Evidence-Based Treatment and Prevention Interventions

NIH supports the development of effective strategies to prevent and treat autoimmune diseases and to translate successful strategies for use in patients. Furthermore, scientists are applying research discoveries made in cancer and other diseases to advance autoimmune disease research. For example, evidence-based cancer therapies that target the protein mTOR may be effective against several autoimmune diseases known as lymphoproliferative disorders, which are associated with an excess production of lymphocytes.

The Immune Tolerance Network (ITN) is a collaborative research effort to study and test new drugs and therapies that induce immune tolerance for the treatment and prevention of autoimmune diseases and other immune-related disorders, while, at the same time, maintaining the body's ability to fight infection. Scientists hope that immune tolerance strategies one day will replace the use of immunosuppressive agents, which broadly reduce the body's immune response and place patients at increased risk for infection. ITN studies related to autoimmunity focus on pancreatic islet transplantation for type 1 diabetes and approaches to slow or reverse progression of autoimmune diseases. Each ITN clinical trial includes a coordinated set of laboratory studies of the genetic, cellular, and immunological mechanisms behind the experimental

treatment. These studies build an understanding of how the body reacts to treatment and may lead to better ways to measure immune tolerance in the immune system.

The NIH focus on treatments for type 1 diabetes extends to a variety of other programs and initiatives. For example, NIH leads an international clinical trials network, the Type 1 Diabetes TrialNet, that tests promising new strategies for prevention in those at elevated risk and early treatment to slow or reverse the course of disease in those newly diagnosed. TrialNet researchers recently found that rituximab, a therapeutic agent currently in use for non-Hodgkin's lymphoma and rheumatoid arthritis, can delay progression of type 1 diabetes in newly diagnosed patients. Several other trials are ongoing through TrialNet, including a trial testing whether oral insulin administration can prevent or delay type 1 diabetes in a group of people who have high levels of antibodies targeted against insulin. These antibodies are markers of preclinical type 1 diabetes.[94]

NIH leads an international clinical trials network, the Type 1 Diabetes TrialNet, that tests promising new strategies for prevention in those at elevated risk and early treatment to slow or reverse the course of disease in those newly diagnosed.

Other research focuses on devising new means to provide insulin to people with type 1 diabetes, who by definition are unable to produce insulin. For example, NIH extramural investigators are working toward the creation of an artificial pancreas. The Clinical Islet Transplantation Consortium is conducting research on transplanting islet cells, the cells from the pancreas that produce insulin, into people whose own islet cells have been destroyed by the autoimmune process that characterizes type 1 diabetes. The consortium focuses on improving the safety and long-term success of methods for islet transplantation.

The NIH Beta Cell Biology Consortium (BCBC)[95] collaboratively pursues research relevant to the development of cell-based therapies for type 1 diabetes, including studies of pancreatic development, the potential of stem cells as a source for making islets, and mechanisms underlying beta cell regeneration. The BCBC has generated research resources, such as animal models and antibodies, which are available to the scientific community.

CombiRx, a double-blind, placebo-controlled Phase III trial, is investigating multiple sclerosis treatment strategies. This study is comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting multiple sclerosis. Investigators are identifying biomarkers that may predict which treatment most likely will benefit a particular patient.

Through the Autoimmunity Centers of Excellence (ACEs), NIH fosters collaboration in prevention and treatment research across scientific disciplines and medical specialties and between basic and clinical scientists. Nine ACEs focus on strategies that induce immune tolerance or regulate the immune system. Researchers also explore the molecular mechanisms underlying the agents evaluated in ACE trials. The enhanced interactions between basic and clinical researchers help to accelerate the translation of research findings into medical applications. ACEs currently support 10 active clinical trials studying treatments for lupus, multiple sclerosis, pemphigus vulgaris, rheumatoid arthritis, and Sjogren's syndrome.

Other NIH-supported initiatives seek to identify and advance novel therapies for autoimmune diseases. For example, the Center for Psoriasis Research Translation pursues research on novel photodynamic therapy for psoriasis. The Sjogren's Syndrome Clinic conducts research on gene therapy and bioengineering that holds promise for the repair or even replacement of salivary glands ravaged by Sjogren's Syndrome.

Addressing the Comorbidities of Autoimmune Diseases

Research to understand, prevent, diagnose, and treat comorbidities that affect many patients with autoimmune diseases can contribute toward reducing the burden of disease. Comorbidities range from the presence of more than one autoimmune

disease to conditions arising from immune attacks on various body tissues or from adverse side effects of autoimmune therapies. For example, the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial tests whether statins—lipid-lowering drugs that reduce serum cholesterol levels—can delay the progression of arterial thickening from atherosclerosis in children diagnosed with lupus.

Patients with type 1 diabetes are at increased risk for many comorbidities related to elevated levels of blood glucose, including eye disorders, nerve and kidney damage, and heart disease. The landmark Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study has shown that intensive control of blood glucose levels reduces the development of these long-term and often life-threatening diabetes complications. This research has revolutionized disease management and led to the recommendation that patients begin intensive therapy as early as possible. These findings also emphasize the importance of investigating new technologies for glucose control and insulin delivery, such as artificial pancreas technologies. [96]

Conclusion

NIH-sponsored research in autoimmune diseases is producing a wealth of knowledge while enhancing collaboration among basic scientists, clinical investigators, and individuals from a host of technical disciplines. Advances in our ability to generate and share genome-wide genotyping data and clinical information from varied cohorts are making it possible for new segments of the general research community to engage in and contribute to research in autoimmune diseases. Over the next several years, NIH will exploit every opportunity to build on its progress in autoimmune disease research, and eagerly looks forward to continuing successes that will yield new knowledge and interventions to improve the lives of all Americans affected by autoimmune diseases.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Basic Immunology

New Program to Focus on Better Defining Human Immune Profiles: In 2009, NIH requested applications for a new research program designed to build on recent advances in immune profiling to measure the diversity of human immune responses to infection or vaccination. Grantees will use a variety of modern analytical tools that will define molecular signatures of specific infections, vaccines, or immune adjuvants, as well as describe steady-state human immune status by a number of parameters. This program is a critical component of the NIH immunology research portfolio. This initiative supports studies that characterize human immune cells and their products isolated from diverse subsets of the population after vaccination, infection, or treatment with adjuvants. NIH will create a grantee consortium that will develop and manage a comprehensive database that consolidates and disseminates information for the scientific community and develop new assays and bioinformatics tools to facilitate productivity. This program, originally intended as an FY 2011 initiative, began 1 year early with ARRA funding.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-040.html
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIAID**) (ARRA)

Progress Toward Immune Tolerance: Since 1999, NIH, with its cosponsor the Juvenile Diabetes Research Foundation International, has supported the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. The ITN is pioneering novel strategies for studying and testing new drugs and therapies against autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based upon principles of immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to "reeducate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. To understand the underlying mechanisms of action of the candidate therapies and to monitor tolerance, the ITN has established state-of-the art core laboratory facilities to conduct integrated mechanistic studies, and to develop and evaluate markers and assays to measure the induction, maintenance, and loss of tolerance in humans. Current ITN studies include pancreatic islet transplantation for type 1 diabetes; approaches to slow or reverse progression of autoimmune diseases such as type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus and other rheumatologic disorders; approaches to treat and prevent asthma and allergic disorders, including food allergy; and therapies to prevent liver and kidney transplant rejection without using lifelong immunosuppressive drugs.

→ For more information, see http://www.immunetolerance.org/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAID**, NIDDK)

Providing Research Resources and Infrastructure

Centers of Research Translation (CORT): The NIH CORTs are designed to bring together basic and clinical research to translate basic discoveries into new drugs, treatments, and diagnostics. Each CORT encompasses at least three projects, including one clinical and one basic research study. The centers are:

- The Center for Translating Molecular Signal Pathways to Orthopaedic Trauma Care studies the biological basis of fracture healing and the efficacy of a potential new treatment, teriparatide, an injectable form of human parathyroid hormone that stimulates new bone formation.
- The Center for Lupus Research investigates the role of different cell types in the origin and development of lupus, markers of disease activity and severity, and new targets for treatment.
- The Center for X-Linked Hypophosphatemic Rickets Research focuses on the various molecular contributors to this genetic form of rickets, and works toward developing new treatments.
- The Center for Research Translation in Scleroderma is studying the molecular basis of scleroderma to understand its underlying causes, using functional genomics and gene networks.
- The Center for Genetic Dissection of Systemic Lupus Erythematosus (lupus) studies mouse models of lupus to identify the genetic background of developmental stages of the disease.
- The Center for New Approaches to Assess and Forestall Osteoarthritis in Injured Joints is developing new methods of forestalling post-traumatic osteoarthritis (PTOA).
- The Center for Psoriasis Research Translation uses a Phase I mechanistic, safety, and preliminary efficacy study to test a novel photodynamic therapy for psoriasis.

→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/11_08.asp
→ For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2007/corts.asp

→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAMS**)

Center for Human Immunology, Autoimmunity, and Inflammation: The Center for Human Immunology, Autoimmunity, and Inflammation (CHI) is a new trans-NIH intramural initiative designed to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiologies, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease. The Center provides unique specific technologies often unavailable to individual laboratories because of cost, complexity, and novelty. The core of CHI is made up of three technology centers. The first center features assays of immune cells and their products, based mainly on a technique known as flow cytometry and similar emerging techniques. The second center contains high-throughput systems technologies, involving the use of new methods for large-scale examination of genes, proteins, enzymes, and/or lipids. It also features advanced biostatical and computer modeling methods for mining these diverse data sets, thereby providing for a deeper understanding of immune function and pathology. The third center is based in protocol development, with staff dedicated to producing methods that efficiently translate to the clinic while considering all of the ethical and regulatory requirements for human research.

→ For more information, see http://www.nhlbi.nih.gov/resources/chi/index.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
→ (I) (**NIAMS**, NCI, NHLBI, NIAID, NICHD, NIDDK, NINDS)

Seeking Solutions for People with Sjogren's Syndrome: Sjogren's syndrome is one of the most prevalent autoimmune disorders, affecting as many as 4 million people in the United States. Nine out of 10 patients affected are female. It is an autoimmune disease that progressively destroys salivary and lachrymal glands. The most common symptoms include dry eyes, dry mouth, fatigue, and musculoskeletal pain. A significant roadblock for moving discoveries ahead in the field of Sjogren's syndrome is the lack of data and biospecimens available for research. Recognizing the problem, NIH spearheaded an effort to establish Sjogren's patient registries at two extramural institutions as well as through its own intramural program. These groups are working together to generate and share with the general research community the genome-wide genotyping data and clinical information from the cohorts enrolled through these efforts. This resource should jumpstart efforts to understand genetic contributions to Sjogren's syndrome and the etiologic overlap with related autoimmune conditions such as lupus and rheumatoid arthritis. In addition to participating in the patient registry and genotyping efforts described above, the Sjogren's Syndrome Clinic, located in the NIH CC, collects systematic clinical and laboratory data on the Sjogren's syndrome (and salivary dysfunction) population. Gene therapy and bioengineering hold promise for the repair or even replacement of salivary glands ravaged by Sjogren's syndrome. More than 300 patient visits occur annually, and the clinic is expanding its patient recruitment to accelerate the conduct of clinical trials that might shed light on this disorder.

→ Korman BD, et al. *Genes Immun* 2008;9(3):267-70. PMID: 18273036.
Roescher N, et al. *Oral Dis* 2009;15(8):519-26. PMID: 19519622. PMCID: PMC2762015.
Nikolov NP, Illei GG. *Curr Opin Rheumatol* 2009;21(5):465-70. PMID: 19568172. PMCID: PMC2766246.
→ For more information, see http://www.sjogrens.org/
→ This example also appears in Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NIDCR**, CC, ORWH)

Understanding the Genetic, Environmental, and Immunologic Factors Contributing to Autoimmune Disease

Genome-Wide Association Studies of Autoimmune Disease Risk: In recent years, genome-wide association studies (GWAS) have transformed the identification of gene regions related to disease risk, through an unbiased analysis of patients with a disease, in comparison with people who don't have it. These GWAS require large numbers of patients and individuals without the disease to obtain statistically significant results. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects, in addition to productive, multisite collaborations across the United States, including international researchers and contributions from the NIH Intramural Research Program. GWAS have yielded important information about disease risk, as well as understanding of disease pathways and potential therapeutic targets, in several autoimmune diseases in the past 2 years. Diseases studied include psoriasis, rheumatoid arthritis, systemic lupus erythematosus (or lupus), ankylosing spondylitis, and type 1 diabetes. Initial results from GWAS require confirmation by replication in additional groups of patients. More detailed localization of disease risk genes can be achieved through comprehensive DNA sequencing of candidate gene regions. New NIH initiatives are supporting these follow-up studies, which are critical to validating GWAS findings.

→ Plenge RM, et al. *Nat Genet* 2007;39(12):1477-82. PMID: 17982456. PMCID: PMC2652744.
Wellcome Trust Case Control Consortium, et al. *Nat Genet* 2007;39(11):1329-37. PMID: 17952073. PMCID: PMC2680141.
Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
Liu Y, et al. *PLoS Genet* 2008;4(3):e1000041. PMID: 18369459. PMCID: PMC2274885.
Nair RP, et al. *Nat Genet* 2009;41(2):199-204. PMID: 19169254. PMCID: PMC2745122.
Barrett JC, et al. *Nat Genet* 2009;41:703-707. PMID: 19430480. PMCID: PMC2889014.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/10_04.asp
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-09-135.html
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2008/Ankyl_Spond_gene.asp
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-123.html
→ For more information, see http://www.nature.com/ng/journal/v41/n6/abs/ng.381.html
→ This example also appears in Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NIAMS**, NCRR, NHGRI, NHLBI, NIAID, NICHD, NIDA, NIDCR, NIDDK)

Lupus: There have been significant advances in identifying disease risk genes for systemic lupus erythematosus (lupus) in recent years. Genome-wide association, linkage analysis, and direct sequencing have revealed genetic variations in lupus patients for molecules involved in immune mechanisms and regulation, inflammation, and vascular cell activities. The disease affects women disproportionately, with female lupus patients outnumbering males nine to one. African American women are three times as likely to get lupus as Caucasian women, and it also is common more in Hispanic, Asian, and American Indian women. These results are being replicated in distinct racial and ethnic populations. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects. Another critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by government agencies, private foundations, and industry. The numerous genes uncovered in these studies reflect the complex expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene specifically is associated with severe forms of lupus that include kidney disease, but not skin manifestations. Methods to analyze patients' blood samples are being developed to group disease-specific variations in gene expression according to pathogenic mechanisms. This system may be used to predict flares of lupus activity in the future and guide individualized treatment. Lupus risk genes also have been discovered on the X chromosome and reproduced in animal models of the disease. These important findings shed light on the female predominance of lupus.

→ Edberg JC, et al. *Hum Mol Genet* 2008 Apr 15;17(8):1147-55. PMID: 18182444.
Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.

International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), et al. *Nat Genet* 2008;40(2):204-10. PMID: 18204446.
Taylor KE, et al. *PLoS Genet* 2008;4(5):e1000084. PMID: 18516230. PMCID: PMC2377340.
Chaussabel D, et al. *Immunity* 2008;29(1):150-64. PMID: 18631455. PMCID: PMC2727981.
Smith-Bouvier DL, et al. *J Exp Med* 2008;205(5):1099-108. PMID: 18443225. PMCID: PMC2373842.
Scofield RH, et al. *Arthritis Rheum* 2008;58(8):2511-7. PMID: 18668569.
Jacob CO, et al. *Proc Natl Acad Sci U S A* 2009;106(15):6256-61. PMID: 19329491. PMCID: PMC2669395.

→ This example also appears in Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*

→ (E/I) (**NIAMS**, NCI, NCRR, NHLBI, NIAID, NIDCR, NINDS)

Immunological Factors in Autoimmune Disease: T Helper Cells: T helper cells are a category of immune cells that orchestrate many complex mechanisms in the immune system by receiving molecular signals and, in return, releasing other molecules that control activities of other cells. As a result, these recipient cells are stimulated, or inhibited, from damaging tissues or destroying pathogenic invaders. Studies in recent years have identified a number of T helper cell (Th) subsets that have fairly specific responses to immune system molecules, and are pivotal to attacks against pathogens, as well as autoimmune reactions—when the immune system aberrantly attacks the body it is supposed to protect. NIH-supported researchers have found that one Th subset (Th17) releases molecules that start a cascade of inflammatory events. The effects of Th17 and other pro-inflammatory cells are balanced by another Th subset, T regulatory cells (Tregs), which dampen inflammation. Job's syndrome is a rare immune disorder, characterized by recurrent and often severe bacterial and fungal infections. Due to a genetic mutation affecting a complex biochemical pathway, patients with Job's syndrome lack interleukin 17 (IL17), the molecule that stimulates Th17 cells. As a result, their immune systems fail to protect them from infections, which have the potential to become life-threatening. On the other hand, patients with psoriasis, an autoimmune skin disease, have high levels of IL17 and very active Th17 cells, which drive inflammation in the skin, leading to scaly, damaged tissue. Additional studies have revealed ways that the body might inactivate Tregs. By understanding the details of failures in biochemical pathways in disease states, scientists may begin to identify ways to correct them therapeutically.

→ Lowes MA, et al. *J Invest Dermatol* 2008;128(5):1207-11. PMID: 18200064.
Milner JD, et al. *Nature* 2008;452(7188):773-6. PMID: 18337720.

→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2008/job_ma.htm

→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2008/08_13b.asp

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*

→ (E/I) (**NIAMS**, NCRR)

Cooperative Study Group for Autoimmune Disease Prevention: The Cooperative Study Group for Autoimmune Disease Prevention was established in 2001 by NIH and its cosponsor the Juvenile Diabetes Research Foundation International as a collaborative network of investigators who focus on understanding immune system dysfunctions that contribute to the development of autoimmune disease, with an emphasis on type 1 diabetes. NIH renewed the Study Group in 2006. It consists of six participating centers that support preclinical research, innovative pilot projects, and clinical studies. Of note, the centers initiated and supported the “Roadmap to Inflammation in the NOD (nonobese diabetic) Mouse” project to identify and characterize genes and proteins involved in the development of diabetes, and study the mechanisms by which diabetes develops. One notable finding suggested by this study is that the development of type 1 diabetes can be characterized by specific differences in how normal genes and gene variants are turned on and off during disease progression. In addition, researchers found patterns of coordinated gene expression that may prove useful as biomarkers of disease onset or progression. Another study, in press, identifies an unusual form of a gene whose expression in specific immune system tissues is associated with type 1 diabetes in both mice and humans.

→ Kodama K, et al. *Clin Immunol* 2008;129(2):195-201. PMID: 18801706. PMCID: PMC2592195.

→ For more information, see http://fathmanlab.stanford.edu/roadmap_study_design.html

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIAID**, NIDDK)

Mercury and Autoimmunity: The causes of autoimmune diseases remain unknown although genetic and environmental factors are believed to play major roles in susceptibility. NIH supports research projects investigating heavy metal-induced autoimmune diseases. The Mercury Induced Autoimmunity Project is working on the role that interferon-gamma plays in the development of induced murine systemic autoimmunity. Another NIH-supported project is investigating links between mercury (Hg) exposure and autoimmune heart disease. This project will assess programming changes that occur during the innate immune response to infection following exposure to Hg, with an overall effect on the progression of Coxsackievirus-induced autoimmune heart disease in mice, and apply the biomarkers from the studies in animals to a Hg-exposed human population in Amazonian Brazil. Another project is investigating the effect of Hg on the neuroimmune system. Studies will investigate the effects of Hg on production of autoantibodies to brain antigens. Antibodies to brain antigens have been demonstrated in patients with different neurological diseases, including neuropsychiatric lupus, Parkinson's disease, schizophrenia, and autism spectrum disorders. An ongoing project is working on development and uses mouse models to understand the relationships between immune system dysfunction and perinatal exposure to environmental toxicants in the development of neurobehavioral disorders such as autism. Mice from this project will be used to assess the effects of perinatal exposure to low levels of methyl mercury (MeHg) on abnormal brain development and behavior mediated by the immune system. These studies should allow insight into the mechanism of induction of immune dysfunction and point to a possible means of therapeutic intervention.

→ Havarinasab S, et al. *Clin Exp Immunol* 2009;155(3):567-76. PMID: 19077085. PMCID: PMC2669534.
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIEHS**)

Psoriasis: Early studies of families of psoriasis patients indicated a genetic susceptibility for the disease. Genome-wide association studies (GWAS) have revealed genetic variations in psoriasis patients for previously identified immune system proteins. New disease risk genes, which are associated with inflammation and immune function, also have been found. Some of these variations occur in or near gene regions associated with other autoimmune diseases, such as rheumatoid arthritis, lupus, and Crohn's disease, although in distinctly independent genes. In addition to variations in genes associated with immune function, GWAS have uncovered differences among psoriasis patients in genes involved with skin differentiation and regulation of inflammation.

→ Liu Y, et al. *PLoS Genet* 2008;4(3):e1000041. PMID: 18369459. PMCID: PMC2274885.
Nair RP, et al. *Nat Genet* 2009;41(2):199-204. PMID: 19169254. PMCID: PMC2745122.
→ This example also appears in Chapter 3: *Genomics*
→ (E) (**NIAMS**, NIDA)

Developing Evidence-Based Treatment and Prevention Intervention

Multiple Sclerosis Research: Although the exact cause of multiple sclerosis (MS) is unknown, recent research supported by NIH has begun to identify genetic variations associated with increased risk for developing the disease. In 2007, a genome-wide association study with NIH support reported the first new genetic risk factors for MS to be identified in more than 20 years, and in 2009, meta-analyses and replication studies revealed additional new susceptibility genes. NIH also funds and conducts basic, translational, and clinical research on disease mechanisms, biomarkers, and treatments for MS. For example, NIH supports a randomized, double-blind, placebo-controlled Phase III trial (CombiRx) comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting MS. The trial will determine whether combination therapy offers an improvement over the partial efficacy of either single treatment; it is the only direct comparison of these commonly used medications that is fully blinded and not

supported by a commercial entity. NIH's Intramural Neuroimmunology Branch is collaborating with this trial to identify biomarkers associated with different clinical and treatment response profiles (BioMS). Such biomarkers may inform predictions about which treatment will most likely benefit a given patient, making this ancillary study an exciting addition to comparative effectiveness research in MS. Intramural investigators also will collaborate with the Swiss pharmaceutical company Santhera in a Phase I/II clinical trial to test the safety and efficacy of idebenone, which may protect against tissue damage, as a potential treatment for primary progressive MS.

- → De Jager PL, et al. *Nat Genet* 2009;41(7):776-82. PMID: 19525953. PMCID: PMC2757648.
- → For more information, see http://clinicaltrials.gov/ct2/show/NCT00211887
- → For more information, see http://clinicaltrials.gov/ct2/show/NCT00325988
- → For more information, see http://clinicaltrials.gov/ct2/show/study/NCT00950248
- → This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- → (E, I) (**NINDS**)

Basic Research on Type 1 Diabetes: NIH vigorously supports basic research on type 1 diabetes. For example, the Beta Cell Biology Consortium (BCBC) collaboratively pursues research relevant to the development of therapies for type 1 and type 2 diabetes, including studying pancreatic development, exploring the potential of stem cells as a source for making islets, and determining mechanisms underlying beta cell regeneration (cells that are the source of insulin production). The BCBC has generated research resources, such as animal models and antibodies, which are available to the scientific community. NIH also has launched initiatives to develop artificial pancreas technology for people with type 1 diabetes. One initiative solicited proposals from the small business community on the development of new technologies to advance progress toward an artificial pancreas. NIH also launched the Type 1 Diabetes Pathfinder Awards, to fund new investigators pursing innovative research on type 1 diabetes and its complications. Research supported through this program focused on areas such as cell replacement therapy, islet encapsulation, and diabetic wound healing.

- → For more information, see http://www.betacell.org
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-001.html
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-08-012.html
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-08-013.html
- → For more information, see http://www2.niddk.nih.gov/Funding/FundingOpportunities/RFA/RFA_T1D_Pathfinder_Announcement.htm
- → This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- → (E) (**NIDDK**, NIBIB, NICHD)

Preclinical and Clinical Research on Type 1 Diabetes: NIH's Type 1 Diabetes TrialNet is an international network that tests strategies for prevention and early treatment of type 1 diabetes. TrialNet recently found that the drug rituximab delayed progression of type 1 diabetes in newly diagnosed patients. To identify environmental triggers of type 1 diabetes, NIH established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium. TEDDY is enrolling newborns at high genetic risk and following them until age 15 to identify environmental triggers. NIH's landmark Diabetes Control and Complications Trial (DCCT) demonstrated that intensive control of blood glucose levels reduced complications of the eyes, nerves, and kidneys in type 1 diabetes patients. Long-term findings from the follow-on Epidemiology of Diabetes Interventions and Complications (EDIC) study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients begin intensive therapy as early as possible. To help patients achieve good glucose control, new initiatives focus on clinical and behavioral research related to new technologies for glucose control and insulin delivery (e.g., artificial pancreas technologies). NIH also supports research on islet transplantation through the Clinical Islet Transplantation Consortium. To provide resources for preclinical development of agents to test in clinical trials, NIH established the Type 1 Diabetes—Rapid Access to Intervention Development program.

→ Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group, et al. *Arch Intern Med* 2009;169(14):1307-16. PMID: 19636033. PMCID: PMC2866072.
Pescovitz MD, et al. *N Engl J Med* 2009;361(22):2143-52. PMID: 19940299.
→ For more information, see http://www.diabetestrialnet.org
→ For more information, see http://www.teddystudy.org
→ For more information, see http://diabetes.niddk.nih.gov/dm/pubs/control/
→ For more information, see http://www.citisletstudy.org/
→ For more information, see http://www.t1diabetes.nih.gov/T1D-RAID/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**, NCCAM, NCI, NIAID, NICHD)

Addressing the Comorbidities of Autoimmune Diseases

Pediatric Rheumatic Diseases: A rare, genetically inherited, inflammatory condition recently was discovered by researchers from NIH and other institutions. DIRA ("deficiency of the interleukin-1 receptor antagonist") patients often are misdiagnosed and do not receive appropriate treatment because their disease is characterized by symptoms seen in many illnesses: recurring episodes of systemic inflammation in multiple tissues, such as skin, bones, and joints. Inflammation is crucial in fighting infections, but uncontrolled, chronic inflammation can cause organ and tissue damage. It was found that DIRA symptoms are caused by a defective gene for a protein (IL-1Ra) that normally inhibits molecular signals for inflammation. Understanding DIRA symptoms and pathogenesis can guide better treatment for the disease, and may help clarify the IL-1Ra gene's role in promoting inflammation in more common diseases. On another front, children with lupus have a significantly increased risk for cardiovascular complications related to premature atherosclerosis, which is a potential source of long-term morbidity and mortality. Statins are drugs that lower cholesterol in blood and decrease the risk for atherosclerosis and cardiovascular disease. Statins also have intrinsic anti-inflammatory properties. The Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial has been testing whether statins can delay the progression of arterial thickening from atherosclerosis in children diagnosed with lupus. Another prospective study of adult and pediatric lupus patients confirmed previous observations, that children have more active disease than adults at the time of diagnosis. Over time, pediatric lupus patients also have more aggressive and severe disease than adult lupus patients.

→ Aksentijevich I, et al. *N Engl J Med* 2009;360(23):2426-37. PMID: 19494218. PMCID: PMC2876877.
Brunner HI, et al. *Arthritis Rheum* 2008;58(2):556-62. PMID: 18240232.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2009/06_03.asp
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAMS**)

NIH Strategic Plans Pertaining to Autoimmune Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

- *NIAMS Long-Range Plan: Fiscal Years 2006-2009*
- *NIAMS Long-Range Plan: Fiscal Years 2010-2014*
- *The Future Directions of Lupus Research*

National Institute of Dental and Craniofacial Research (NIDCR)

- *NIDCR Strategic Plan*
- *NIDCR Implementation Plan*

National Institute of Allergy and Infectious Diseases (NIAID)

- *NIAID: Planning for the 21st Century — 2008 Update*
- *NIAID Plan for Research on Immune Tolerance (1998)*
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- *Expanding Horizons of Health Care: Strategic Plan 2005-2009*

Trans-NIH Plans

- *NIH Autoimmune Diseases Coordinating Committee: Autoimmune Diseases Research Plan*
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- *NIH Action Plan for Transplantation Research (2007)*
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- *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*
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- Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases
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Chronic Diseases and Organ Systems

When someone has a chronic disease, doctors may use a variety of tools—such as blood tests, X-rays, and more expensive or invasive technologies—to assess whether the disease is progressing or if the person is responding to treatment. The physical changes that these tests show, however, do not always correlate with patients' subjective experiences of symptom severity and frequency, emotional and social well-being, and perceived level of health and functional ability.

Measurement of subjective patient-reported outcomes is particularly important in clinical trials in which two treatments may be comparable in limiting or curing disease but have different effects on symptoms, functioning, or other aspects of patients' quality of life. Recognizing the importance of interventions that improve the day-to-day lives of people who have chronic diseases, NIH has created the Patient-Reported Outcomes Measurement Information System (PROMIS) initiative to develop an analytic tool that researchers can use to assess systematically and objectively several factors that are meaningful to patients from different walks of life who have various chronic diseases.

Already, investigators have found that a short, 10-question survey, administered using the computer adaptive testing system of PROMIS, outperforms the most commonly used, paper-based, self-reporting assessment tool for arthritis disability. As the PROMIS initiative enters its second phase, researchers will further validate and evaluate PROMIS' usefulness in NIH-supported clinical trials; facilitate adoption of PROMIS by the clinical research community; and build partnerships to sustain PROMIS once the second phase of NIH support is complete. The ultimate goal is for PROMIS to fulfill its "promise" of reliably integrating into clinical testing those outcomes that have the greatest effects on patients' lives.

Introduction

Chronic diseases are defined by the U.S. Department of Health and Human Services as conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living. Chronic diseases place a considerable burden on the U.S. health care system, the national economy, and the health and lives of individual patients and their families. Not all chronic diseases are fatal, and not all fatal conditions are chronic. Nonetheless, 7 of every 10 Americans who die each year—more than 1.7 million people—succumb to a chronic disease.[97] Health-damaging behaviors such as drug use (e.g., tobacco, excessive alcohol, or other drug), lack of physical activity, and poor eating habits, contribute to many chronic diseases, whereas others may result from the long-term effect of early exposure to toxins or other environmental factors, especially in individuals with a higher genetic risk of disease. A shared aspect of many chronic diseases is chronic pain and other disease-associated disability that interferes with quality of life: approximately one-fourth of Americans living with a chronic illness—fully 1 in 10 Americans overall—experience significant limitations on daily activities due to their condition. As many as 75 million Americans suffer from 2 or more concurrent chronic conditions,[98] placing them at risk not only for worse overall health but also for significant financial burden, including higher prescription drug and total out-of-pocket health care spending. Many chronic diseases that are common in the United States—such as type 2 diabetes, obesity, and heart disease—also have a substantial impact on global morbidity and mortality.

Many of the most burdensome chronic diseases develop over time and become more prevalent with age (e.g., osteoarthritis, chronic kidney disease, vision loss); less commonly, chronic disease may manifest from birth as a result of one or more faulty genes (e.g., sickle cell anemia, hemophilia) or at other times during childhood (e.g., allergies, asthma). Some chronic diseases are common in the U.S. population, as in the case of heart disease, which is the leading cause of death, while others are relatively rare, such as cystic fibrosis, which affects approximately 30,000 Americans. Certain chronic diseases represent growing public health issues, such as the increases in obesity and type 2 diabetes in children and adults.

Some chronic diseases and conditions may affect more than one organ. For example, diabetes can affect the pancreas, heart, kidneys, eyes, and nerve endings in the limbs. In addition, some chronic diseases, including addiction and other mental illnesses, have significant mental, psychological, and behavioral components. For these reasons, modern medicine requires an integrated understanding of the complex interactions among multiple organs, the nervous system, the circulatory system, the immune system, and the endocrine system. Thus, research to combat chronic illness involves significant trans-NIH collaboration in addition to the mission-specific work of each IC. NIH supports basic research on both normal and disease states of organ systems to understand the initiation and progression of chronic diseases, as well as translational and clinical research on new biomedical and behavioral strategies to prevent, preempt, diagnose, treat, and cure these diseases. The ultimate goal is to reduce or eliminate morbidity and mortality while improving quality of life for those living with these often debilitating conditions.

This section provides information about NIH's activities related to a number of major chronic diseases, as well as research on aspects of the function of various organ systems. Additional major chronic diseases are discussed in this chapter in the sections "Cancer" (cancers of all organs and tissues, including blood), "Neuroscience and Disorders of the Nervous System" (e.g., Parkinson's disease, Alzheimer's disease, autism, and epilepsy), "Autoimmune Diseases" (e.g., lupus, multiple sclerosis, type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease), and "Infectious Diseases and Biodefense" (e.g., HIV/AIDS and hepatitis). Because some people with certain chronic diseases require transplantation to replace a diseased organ or tissue, organ transplantation research and the related issue of establishing immune tolerance to transplanted organs are highlighted in this section. Research on complementary and alternative medicine (CAM) approaches to combating chronic disease also is discussed. NIH supports research to reduce the pain associated with long-term diseases and to find innovative and effective forms of palliative care to relieve disease symptoms. Some of these efforts are highlighted in this section; more information on NIH pain research also can be found at the NIH Pain Consortium website.

Burden of Illness and Related Health Statistics

The prevalence and burden of chronic diseases are substantial. About 133 million Americans—nearly 1 in 2 adults—live with at least 1 chronic illness, and as noted above, each year 1.7 million people in the United States die from a chronic disease.[99] Chronic disease disables or limits activity for almost 12 percent of all adults, including more than one-third of adults ages 65 and older.[100] Notably, the percentage of U.S. children and adolescents with a chronic health condition has increased significantly, from 1.8 percent in the 1960s to more than 7 percent in 2004. Furthermore, the increasing prevalence of patients with 1 or multiple chronic diseases has a significant impact on health care delivery and the economy: More than 75 percent of health care costs are due to chronic conditions.[101]

Worldwide, the burden of chronic disease is increasing rapidly. By 2015, chronic diseases will be the most common cause of death even in the poorest countries. In 2005, chronic diseases contributed approximately 60 percent of the 58 million total deaths in the world and almost three-quarters of the burden of disease (measured in disability-adjusted life-years) in those ages 30 or older.[102]

Worldwide, the burden of chronic disease is increasing rapidly. By 2015, chronic diseases will be the most common cause of death even in the poorest countries.

More detailed data on the U.S. burden of many of the major chronic illnesses are provided at the end of this section.

NIH Funding for Chronic Diseases and Organ Systems Research

Currently, NIH does not collect the data necessary to provide an aggregate figure for expenditures on chronic diseases and organ systems research, although this capacity is expected to be developed in the future for integration with RCDC. The table at the end of this chapter provides funding estimates for many of the areas of research associated with chronic

diseases and organ systems (see *Estimates of Funding for Various Research, Condition, and Disease Categories*). Because of overlap among the areas of research listed in the table, and because research on chronic disease and organ systems may account for only a portion of the funding for a given area, the figures in that table cannot be used to provide an aggregate number.

About Various Chronic Diseases and Conditions

Links to detailed information on many specific chronic health conditions can be found at http://health.nih.gov. Following are examples of chronic diseases and conditions addressed by NIH-funded research, with links to major associated research programs and NIH research fact sheets.

Cardiovascular Diseases: Heart disease is the leading cause of death in the United States.[103] Coronary heart disease, the most common type of heart disease, occurs when plaque builds up in the arteries that supply blood to the heart muscle. Coronary heart disease can cause angina (chest pain) or a heart attack and, over time, contributes to serious disability or death. Other chronic, serious cardiovascular conditions include hypertension, heart failure, atrial fibrillation, and peripheral arterial disease. Additional, and sometimes rare, cardiovascular disorders include Marfan syndrome, a connective tissue disorder that affects the heart and blood vessels and other parts of the body; long QT syndrome, a disorder of the heart's electrical activity that may cause a sudden, uncontrollable, and dangerous heart rhythm; and congenital heart defects.

Lung Diseases: Chronic obstructive pulmonary disease, the fourth leading cause of death in the United States,[104] causes airflow obstruction in the lungs that makes breathing difficult. Asthma, the most common chronic disease of childhood, is characterized by inflamed and narrowed airways. Rare lung diseases include cystic fibrosis, an inherited disease that affects multiple organs, and idiopathic pulmonary fibrosis, in which lung tissue becomes thick and stiff, resulting in loss of function.[105]

Diabetes Mellitus: Diabetes is characterized by abnormally high levels of glucose (sugar) in the blood. It can be caused by either autoimmune destruction of cells in the pancreas (type 1) or the inability of tissues, such as the muscles and liver, to use insulin properly (type 2). Diabetes can result in complications such as heart disease, stroke, hypertension, and nerve damage. It also is the leading cause of kidney failure and nontraumatic lower limb amputation in the United States and of new cases of blindness among working-age Americans. Women with no prior history of diabetes who develop high blood sugar levels while pregnant are said to have gestational diabetes mellitus (GDM). GDM affects 3-8 percent of all pregnant women and can have long-term health consequences for both the fetus and the mother, including an increased risk of developing type 2 diabetes later in life.[106]

Obesity: Obesity, which has risen to epidemic levels in the United States, is a chronic, relapsing health problem caused by an interaction of genes, environment, and behavior. A common measure of overweight and obesity in adults is body mass index (BMI)—a calculation based on height and weight. For most people, BMI correlates with their amount of body fat and serves as an indicator of weight-related health risks. An adult with a BMI between 25 and 29.9 is considered overweight, whereas an adult with a BMI of 30 or higher is considered obese. Although BMI numbers are interpreted differently for children, their rates of overweight and obesity have risen dramatically in recent years. Obesity increases the risk of other chronic conditions, including type 2 diabetes, heart disease, certain cancers, osteoarthritis, liver and gallbladder disease, urinary incontinence, and sleep apnea, and also is associated with depression.

Kidney Diseases: Chronic kidney disease is the progressive, permanent loss of kidney function that can result from physical injury or from a disease that damages the kidney such as diabetes, high blood pressure, or polycystic kidney disease. Patients with advanced chronic kidney disease may progress to irreversible kidney failure and require immediate, life-saving dialysis or a kidney transplant. Chronic kidney disease is a growing problem in the United States.

Digestive and Urologic Diseases: Diseases of the digestive system involve many organs (e.g., intestines, stomach, liver, gallbladder, and pancreas) and include disorders such as irritable bowel syndrome, ulcerative colitis, Crohn's disease, celiac disease, peptic ulcer disease, gallstones, gastroesophageal reflux disease, and chronic pancreatitis. Illnesses of the genitourinary tract are similarly diverse and include chronic prostatitis, benign prostatic hyperplasia, interstitial cystitis and painful bladder syndrome, urinary incontinence, and urinary tract infections.

Liver Diseases: Chronic forms of liver disease include chronic viral hepatitis (B and C), alcoholic and nonalcoholic fatty liver disease, genetic diseases such as hemochromatosis, and autoimmune diseases such as primary sclerosing cholangitis. Significant liver injury sometimes can result from adverse reactions to medical drugs and other compounds. Although many organ systems may be damaged by chronic alcohol use, alcoholic liver disease is the leading cause of death from excessive and long-term alcohol consumption.

Blood Diseases: Chronic anemias result from a deficiency of red blood cells or an abnormality in hemoglobin production, as is the case with sickle cell diseases and Cooley's anemia. Patients can experience pain, fatigue, and other serious health problems. Chronic inherited bleeding disorders, such as hemophilia and von Willebrand disease, leave patients at risk for uncontrollable bleeding.

Musculoskeletal Disorders: Osteoarthritis, the most common form of arthritis, is a degenerative disease caused by the breakdown of cartilage, leading to pain, swelling, and stiffness in joints. Osteoporosis, another musculoskeletal disease that causes significant disability, occurs when bones become thin, weak, and fragile. Other chronic bone diseases include osteogenesis imperfecta, a genetic disease that causes bones to become brittle and break for no known reason, and Paget's disease of bone, in which bones grow larger and weaker than normal. Many older adults develop chronic low back pain as the bones in the spine change shape and the spinal ligaments that hold the bones in place weaken. Soft tissue sprains and strains can begin as acute injuries but often cause chronic problems because the injured ligaments, tendons, or muscles never fully recover and are susceptible to re-injury.

Skin Disorders: Skin, the largest organ of the body, separates the internal organs from the outside environment, protects against bacteria and viruses, regulates body temperature, and provides sensory information about surroundings. The most common type of eczema—inflammation of the skin—is atopic dermatitis, which is characterized by dry, itchy skin.

Vision and Hearing Loss: The eyes and ears contain specialized nerve cells for sensing light and sound and for relaying these signals to the brain. Death or damage to light-detecting cells (e.g., retinopathy, retinitis pigmentosa) or to cells of the optic nerve (e.g., glaucoma) can lead to chronic impairment of vision. Likewise, sensorineural hearing loss is caused by death or damage to the auditory nerve or to the sound-detecting cells of the inner ear. Many common auditory and visual disorders are age-related and can reduce independence and quality of life in the elderly. These include presbycusis (age-related hearing loss), age-related macular degeneration (loss of central vision), and cataract (clouding of the lens of the eye).

Dental and Craniofacial Disorders: Periodontal disease is a disorder of the gingiva and tissues around the teeth. It varies in severity but can lead to bleeding, pain, infection, tooth mobility, and tooth loss. Periodontal disease can affect other organs and has been linked to cardiovascular disease, diabetes, and pulmonary disease. Temporomandibular joint and muscle disorders, commonly called TMJD, are a group of conditions that cause pain and dysfunction in the jaw joint and the muscles that control jaw movement. The primary symptom of these disorders is pain, which can become permanent and debilitating.

Mental Illness: Mental disorders are the leading cause of disability in the United States and Canada. In contrast to many other chronic medical conditions, mental disorders typically begin at an early age, usually before the age of 30. Mental disorders, such as schizophrenia and mood disorders including depression and bipolar disorder, are increasingly recognized as chronic medical illnesses of young people. Mental illness also can coexist with a number of other chronic diseases. For example, major depressive disorder, a significant contributor to disability worldwide, can be triggered by

chronic diseases such as cancer or stroke in those who are at risk for developing the disorder. Conversely, depression is associated with an increased risk for other diseases such as coronary heart disease and drug addiction.

Addiction to Alcohol and Other Drugs of Abuse: The frequent co-occurrence of mental disorders with alcohol dependence and other substance use disorders, including nicotine addiction, makes treating both disorders crucial, albeit challenging. Addictions to alcohol and other drugs of abuse are chronic diseases that have both physiological and behavioral components.

Chronic Pain and Palliative Care: Pain and palliation—care to alleviate the symptoms of disease and improve quality of life without actually curing the disease—are issues associated with many chronic diseases, regardless of the organ system affected. Pain is cited as the most common reason Americans access the health care system; it is a leading cause of disability; and it is a major contributor to health care costs. Low back pain is among the most common complaints, along with migraine or severe headache, and joint pain, aching, or stiffness. Joint pain is most commonly experienced in the knee.[107]

Summary of NIH Activities

NIH invests significant resources in the study of chronic diseases. The diverse NIH research portfolio broadly encompasses research on the normal physiology of all organ systems in the body; studies of rare and common diseases in both children and adults; development of devices and technologies for disease detection and diagnosis; evaluation of strategies for prevention and treatment that might be based on pharmaceuticals, behavioral modification, surgical techniques, mechanical devices, or other approaches; and translation of research results into real-world applications or resources for the benefit of patients who live with chronic diseases every day. This section highlights key examples of challenges, progress, and emerging opportunities in NIH-supported research on chronic diseases and organ health.

Understanding Fundamental Mechanisms of Organ Health and Disease

NIH supports a diverse portfolio of basic research to understand the molecular and cellular mechanisms of human physiology in health and disease. Basic science discoveries are critical for generating new insights into disease triggers and risk factors, identifying new targets for therapy, and developing innovative strategies and advanced technologies to prevent, detect, diagnose, and treat chronic diseases and organ damage. For example, scientists have discovered a protein, Roundabout4 (Robo4), which blocks the activity of vascular endothelial growth factor (VEGF). Abnormal activation of VEGF triggers neovascularization—the pathologic growth of new blood vessels—that is characteristic of eye diseases such as age-related macular degeneration and diabetic retinopathy. Thus, Robo4 presents a new target for the development of therapies to prevent or delay vision loss in patients with vascular eye disease. Advances in neurobiology have revealed a connection between brain function and obesity that could point to new weight loss strategies. For example, researchers have discovered that, in response to fat intake, the small intestine releases a factor that subsequently enters the brain and suppresses appetite in rats.

New findings in alcohol research have uncovered molecular mechanisms involved in both the detrimental and beneficial effects of alcohol. Experiments in fruit flies pointed to a role for the epidermal growth factor receptor (EGFR) pathway in mediating sensitivity to alcohol. Researchers also showed that FDA-approved drugs that block the EGFR pathway increased alcohol sensitivity in mice and decreased alcohol consumption in rats, suggesting that these existing drugs might be useful as treatments for alcohol use disorders in humans. Other studies revealed the endocannabinoid pathway as a factor in both diet- and alcohol-induced fatty liver and its metabolic consequences. In addition, researchers identified a molecular pathway that could explain how moderate levels of alcohol consumption protect the heart from ischemic injury,

a leading cause of death in developed countries. Development of drugs that target these pathways could lead to new treatments for fatty liver and cardiac ischemia, respectively.

At the level of cellular biology, NIH-supported researchers are making progress in understanding the role of specific cell types in health and disease. For example, scientists have demonstrated that hematopoietic stem cells (HSCs) from bone marrow can direct the differentiation of osteoblasts (cells that build bone) from precursor cells. This finding suggests that HSCs might represent a therapeutic target for treating a variety of bone defects, including osteoporosis, nonhealing bone and tooth defects, and congenital bone abnormalities. In another example, for many years, scientists believed that metabolically active brown fat could be found only in human infants and in hibernating mammals. Recent findings from NIH-supported research have overturned this longstanding paradigm by revealing that brown fat cells do in fact persist in adult humans. In contrast to white fat cells that store fat, brown fat cells burn fat to generate heat and, therefore, present a novel target for obesity and weight control therapies.

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Some chronic diseases are associated with the presence of infectious agents that may be either a consequence or a cause of the disease. For example, patients with atopic dermatitis, a common form of eczema, have high levels of bacteria, such as *Staphylococcus aureus*, on their skin, and these patients experience frequent skin infections. Researchers have learned that atopic dermatitis patients exhibit high levels of Th2 cytokines in their skin that prevent the release of an antimicrobial protein that would normally kill the bacteria. Other researchers are studying *Porphyromonas gingivalis*, a bacterium that causes severe, chronic periodontal disease. Using a mathematical technique known as flux-balance analysis, scientists developed a metabolic network map of *P. gingivalis*. This map provides an important tool for predicting how the bacterium would react to perturbation of specific genes or metabolic pathways and will accelerate research to discover new antibacterial drug targets.

NIH is developing new initiatives to capitalize on major breakthroughs and stimulate basic research that will fill gaps in our understanding of a variety of chronic diseases. For example, the NIEHS Director's Challenge Program is advancing research on diseases associated with oxidative stress. The program supports highly collaborative, multidisciplinary teams to study the role of specific genes involved in oxidative stress-induced diseases. Although the program initially will focus on bronchopulmonary dysplasia and retinopathy of prematurity—chronic diseases that affect very low birth weight infants—support for this line of research has the potential to impact a range of diseases, including asthma, cancer, cardiovascular diseases, and neurodegenerative diseases.

Animal models that faithfully mimic human disease or aspects of disease are important tools for understanding fundamental disease mechanisms and for developing new strategies for prevention and treatment. NIH-supported researchers developed a pig model that lacks or has mutations in CFTR, the gene responsible for cystic fibrosis in humans. This new large animal model provides extraordinary opportunities to understand the development of cystic fibrosis in childhood and to test potential therapies. New research grants have been funded to support multidisciplinary research on this unique model of cystic fibrosis.

Detecting and Diagnosing Chronic Disease

Early detection of a chronic disease or organ damage can benefit patients and improve understanding of disease progression in ways that could lead to new strategies for disease prevention. NIH supports research on new methods and technologies for early, accurate, and less invasive detection of chronic diseases. Among the benefits of early disease detection is the opportunity it affords patients to begin to take measures that might prevent disease progression or

otherwise improve health outcomes. For example, NIH supports research aimed at evaluating the most effective strategies to improve screening methods to identify youth and adults who have or are at high risk for developing alcohol and other drug use disorders. Related studies focus on understanding what factors, such as the role of parents or families, increase the use and effectiveness of alcohol screening and intervention programs in youth. NIH also provides tools to facilitate the implementation of screening and brief intervention in primary care settings. For example, the NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test, or NM ASSIST is a Web-based tool that guides clinicians through a short series of questions for patients and, based on a patient's responses, generates a substance involvement score that suggests the level of intervention needed. The tool also provides links to resources for conducting a brief intervention and treatment referral, if warranted.[108]

One benefit of early detection is that it might lead to new insights into the natural history of a disease. NIH and NASA researchers have developed an imaging device that allows clinicians to measure the loss of alpha crystallin protein in the eye, a process that precedes age-related cataract formation. This new imaging technology will help researchers better understand the development of cataracts, a leading cause of adult blindness, and could point to new strategies for prevention of vision loss in cataract patients.

Scientists are developing a new technology that combines magnetic resonance imaging with sound waves to measure the "stiffness" of an internal organ, which could provide diagnostic information without the need for organ biopsy or other invasive techniques.

In addition to early detection, accurate diagnosis of disease is critical to ensuring that a patient's disease is treated promptly and appropriately. For example, scientists are developing a new technology that combines magnetic resonance imaging (MRI) with sound waves to measure the "stiffness" of an internal organ, which could provide diagnostic information without the need for organ biopsy or other invasive techniques.

Often patients, especially those with rare diseases or conditions, seek help from multiple physicians and other health care providers over many years without receiving a definitive diagnosis. NIH has launched a new clinical research program, the Undiagnosed Diseases Program (UDP), to evaluate patients with longstanding undiagnosed disorders. The UDP capitalizes on the combined knowledge of a team of NIH scientists and medical specialty experts to assist patients who have unknown disorders in achieving an accurate diagnosis, as well as to discover new diseases that provide insight into human biology. In its first year, 158 patients with undiagnosed medical conditions were accepted into the program.

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Identifying Risk and Preventing Chronic Disease

A person's risk for developing a chronic disease can depend on multiple factors that include genetic or inherited traits, exposure to environmental toxins, or modifiable behaviors such as diet, smoking, physical activity, or stress. Many chronic diseases are known to result from interactions among genetic, environmental, and behavioral factors, although for most diseases the exact nature of those interactions and the relative importance of the various risk factors remain poorly understood. NIH supports research to identify all types of risk factors, understand the contribution of risk factors to the mechanisms of disease, and apply knowledge of those factors to develop strategies for modifying risk and preventing disease.

NIH-supported researchers have made significant progress in discovering a diversity of risk factors for common chronic diseases. NIH-supported Transdisciplinary Tobacco Use Research Centers have explored many variables associated with vulnerability to tobacco addiction and/or cessation, including genetic, familial, cultural, environmental, and comorbidity

factors. Research on the effects of environmental exposures has found that certain pesticides are associated with increased risk of type 2 diabetes in individuals who are licensed pesticide applicators. This elevated risk was independent of the age, state of residence, or body mass index of the individual. Several cohort studies of osteoporosis have searched for factors that predict risk of bone fracture in older Americans. For example, researchers using data from the Framingham Osteoporosis Study observed that higher vitamin C consumption is associated with fewer hip fractures, while researchers from the Women's Health Initiative showed that low blood levels of vitamin D are associated with higher risk of hip fracture. The identification of modifiable risk factors, such as vitamin intake, in these and related studies can inform strategies for diagnosis, prevention, and treatment of osteoporosis in elderly individuals who are most vulnerable to fracture.

Specific population groups as defined by age, sex, race, ethnicity, or an array of other characteristics appear to be at higher risk for some chronic diseases. For these reasons, NIH supports large epidemiologic and clinical studies to identify genetic and nongenetic risk factors in defined populations.

Like osteoporosis, many chronic diseases are associated with a large number of risk factors, some of which have small or variable effects in any single individual. In addition, specific population groups as defined by age, sex, race, ethnicity, or an array of other characteristics appear to be at higher risk for some chronic diseases. For these reasons, NIH supports large epidemiologic and clinical studies to identify genetic and nongenetic risk factors in defined populations. Examples of large population studies to identify risk factors for chronic diseases include:

- Multiple chronic diseases, including heart disease, stroke, asthma, chronic obstructive pulmonary disease, sleep disorders, dental disease, hearing loss, diabetes, kidney disease, liver disease, cognitive impairment, and others, in people of Hispanic/Latino heritage living in the United States (Hispanic Community Health Study)
- Cardiovascular disease in men and women from four ethnic groups—White, African American, Hispanic, and Chinese (Multi-Ethnic Study of Atherosclerosis)
- Cardiovascular disease in American Indian families (Strong Heart Study)
- Coronary artery disease in Alaskan Natives (Genetics of Coronary Artery Disease in Alaska Natives Study)
- Cardiovascular disease in African American and White young adults who were between 18 and 30 years of age when the study began in 1985 (Coronary Artery Risk Development in Young Adults Study)
- Chronic obstructive pulmonary disease in current and former smokers (Genetic Epidemiology of COPD study)
- Alcohol dependence in extended families that are densely affected by alcoholism (Collaborative Study on the Genetics of Alcoholism)
- Glaucoma in adults (NEI Glaucoma Human Genetics Collaboration)
- Diabetes in youth under 20 years of age in varying ethnic and racial groups (Search for Diabetes in Youth Study)
- Diabetes in families with multiple members affected (Type 1 Diabetes Genetics Consortium) and several studies of type 2 diabetes, including cohorts from European and Scandinavian populations (e.g., Finland-US Investigation of NIDDM Genetics, Diabetes Genetics Replication and Meta-analysis Consortium) and from multiple ethnic groups (The Diabetes Prevention Program, or DPP)
- Breast cancer, uterine fibroids and endometriosis, rheumatoid arthritis, thyroid disease, asthma, cardiovascular disease, osteoporosis, Parkinson's disease, age-related cognitive decline, and other diseases in sisters of women who have had breast cancer (The Sister Study: Environmental Risk Factors for Breast Cancer and Other Diseases)

Many chronic diseases have complex genetic contributions, such that susceptibility for a given disease can be influenced by different genes in individual patients or groups of patients. Scientists identified variants of the *MYH9* gene that are associated with chronic kidney disease (CKD) in African Americans and that result from conditions other than diabetes. This finding suggests that CKD may proceed along different paths depending on whether diabetes or another condition underlies the disorder. In the long term, researchers might be able to predict a person's risk for CKD or their potential to respond to specific therapies depending on whether they carry *MYH9* variants that are associated with the disease.

By understanding the risk factors associated with specific chronic diseases, researchers can design interventions that may prevent or delay onset of these diseases in susceptible individuals. Prevention strategies can address biological, environmental, behavioral, or psychological factors in the development of disease and may be tailored to meet the needs of specific groups or settings. For example, the rate of type 2 diabetes and obesity is increasing among both adults and children in the United States. Previously, the Diabetes Prevention Program (DPP) showed that either lifestyle modification to promote modest weight loss or treatment with the diabetes drug metformin could prevent or delay the onset of type 2 diabetes in at-risk adults in all participating ethnic groups. A follow-up study, the Diabetes Prevention Program Outcomes Study (DPPOS) is assessing the long-term durability of the DPP interventions, as well as their impact on preventing cardiovascular disease.

NIH is committed to translating the results of carefully controlled clinical trials into strategies for disease prevention and control that will benefit the general public. For example, researchers are evaluating the effectiveness of the Diabetes Prevention Program (DPP) lifestyle intervention in real-world settings. A recent pilot study suggests that using YMCAs may be a low-cost way to deliver a lifestyle intervention proven to prevent or delay type 2 diabetes to large numbers of people at risk for the disease in the United States. This type of translational research is critical for validating a cost-effective method for prevention of type 2 diabetes on a population-wide scale, especially for those from minority populations that are disproportionately affected by this disease.

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Many chronic illnesses are largely preventable through behavioral changes. For example, tobacco use, insufficient physical activity, and poor eating habits are implicated in many of the most common chronic diseases, including cardiovascular disease, type 2 diabetes, and chronic obstructive pulmonary disease. However, changing unhealthy behaviors can be challenging for many people. To facilitate a more comprehensive understanding of aspects of behavior change across a variety of disciplines, the trans-NIH Committee on the Science of Behavior Change (SOBC) has been established. In June 2009, NIH brought together experts in the fields of basic and applied behavioral sciences, genetics, economics, and methodology with the goal of advancing an NIH-wide agenda on the science of behavior change. The main topics of discussion were acquiring and preventing particular behaviors, changing existing behaviors, and maintaining desirable behaviors. The committee will use ideas generated from the meeting to develop new interdisciplinary initiatives in behavior change research.

Prevention of chronic diseases in children and other vulnerable populations is a major focus of NIH research. For example, clinical research trials to prevent type 2 diabetes and obesity in children are underway. One such study, HEALTHY, is testing a multifaceted approach for prevention of type 2 diabetes risk factors in middle school children. Components of the HEALTHY prevention strategy include changes to school food services and physical education classes, behavioral changes, and communications campaigns. Other researchers are assessing whether development of peanut allergies in at-risk infants and very young children could be prevented by early and regular consumption of peanut-containing snacks. Studies on the prevention of drug abuse in children and adolescents are evaluating innovative approaches, such as physical activity to counter drug use, interactive Web-based technologies to engage young people, and brain imaging results to better target media messages. The NIH Rapid Response Program supports research to prevent and reduce alcohol use among college students. A variety of prevention approaches are being explored, such as residential learning communities, peer-facilitated alcohol interventions, freshman parent-student initiatives, alcohol screening in college health clinics, and others.

U.S. military personnel, veterans, and their families are at high risk for the onset, exacerbation, or relapse of substance abuse and other mental health problems. NIH has launched initiatives to encourage collaborative research on prevention of alcohol, drug, and tobacco abuse, as well as associated problems such as post-traumatic stress disorder, traumatic brain

injury, sleep disturbances, and relationship violence, in military members and their families. The role of trauma and stress in the onset of substance use and abuse in this population is a particular area of research focus.

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NIH awareness campaigns and educational materials are critical tools for keeping the public informed of new findings in prevention research. A recently updated guide, titled *Exercise and Physical Activity: Your Everyday Guide from the National Institute on Aging*, reviews the benefits of physical activity and exercise in combating chronic conditions in older adults. The *Guide* provides specific activities and exercises that can be tailored to an individual's strength and skill level. Additional awareness campaigns and education materials on chronic diseases are described in the section "*Chapter 3: Health Communication and Information Campaigns and Clearinghouses.*"

Depression frequently occurs among individuals with other medical conditions, such as heart disease, diabetes, and Parkinson's disease. Ongoing NIH-supported research on early detection, prevention, and treatment of depressive disorders—and their relationship to other chronic diseases—can help identify ways to reduce the years lost due to disability as a result of comorbid depression.

Treating Chronic Disease and Comorbidities

Once established, chronic diseases require long-term interventions that frequently involve a combination of medical, surgical, behavioral, or other treatments. For some diseases without effective therapies, symptom management to improve quality of life is the only option. Even when therapies are available for a given disease, those therapies might not be appropriate for all patients. For example, drugs or other treatment approaches used in adult patients have not always been proven to be safe for use in children. Other therapies that have been developed based on specific molecular pathways or genetic mutations might have variable efficacy in individual patients with different genetic backgrounds.

Treatment of comorbid chronic disease presents particular challenges. Notably, individuals with multiple chronic conditions are more likely to endure poor functional status, unnecessary hospitalizations, adverse drug events, duplicative tests, and conflicting medical advice. NIH is committed to addressing the needs of Americans with two or more chronic medical conditions. For example, in 2005, NIH solicited applications on research supporting planning projects for clinical trials that establish a scientific basis for future interventions to improve health outcomes related to interactions of multiple co-occurring conditions in elderly patients. Projects funded under this initiative were active during FY 2008 and included Patient-Centered Care Management for Seniors with Multiple Morbidities, Walking Activity and the Burden of Multiple Morbidities, Nursing Home Comorbid Depression Care Management, Osteoporosis in Women with Rheumatoid Arthritis, and Tailored Clinical Trials for Hypertension and Fall Risk. In another example, scientists are studying how best to treat people with both cystic fibrosis and diabetes. New treatments for cystic fibrosis are helping people live much longer, but this has resulted in an increasing number of people with the disease developing cystic fibrosis-related diabetes. New research has shown that aggressive insulin therapy, begun earlier in the course of diabetes than previously recommended, can help many people with cystic fibrosis-related diabetes maintain their body weight and avoid the excess mortality associated with this comorbidity.

To address the critical medical needs of the American public, NIH pursues a vigorous research agenda to identify, develop, and validate innovative treatments for chronic diseases and organ damage that are safe, efficacious, and cost-effective.

An essential first step in the development of new medical therapies for chronic diseases is the identification of molecules with a desired biologic activity. Preclinical studies in animal models are then conducted to examine safety and efficacy of

novel compounds before they are tested in people. NIH supports research that fills important gaps in preclinical drug development that currently are not being addressed by the pharmaceutical industry. For example, laboratories have been established to screen molecules that hold promise for the treatment of alcohol dependence. Other researchers are developing medications for stimulant, cannabis, inhalant, or polysubstance abuse. Such medications might act by diminishing conditioned responses, improving cognitive function (thereby facilitating engagement in cognitive-behavioral therapy), or modifying the brain's response to stress, one of the primary triggers for relapse in people recovering from addiction. Once a candidate drug has been chosen, animal studies can provide a preliminary estimation of risks and benefits. For example, researchers have identified two drugs that increase fat-burning muscle and improve endurance in mice. These drugs could represent new treatments for certain muscle disorders, frailty, obesity, or other conditions that could be improved by exercise. In another example, NIH supports Molecular Therapy Centers for Cystic Fibrosis and Other Genetic Metabolic Diseases that are developing new therapeutics for cystic fibrosis and related diseases.

In addition to developing novel drugs, NIH investigators are exploring the potential of using drugs with known safety profiles that have been approved for one condition to treat an unrelated disease. For example, animal studies suggest that fenoterol, a drug used for the treatment of pulmonary disease, might be beneficial in patients with congestive heart failure. Modafinil, approved to treat narcolepsy, may be useful in improving cognitive dysfunction, often a barrier to engaging drug abuse patients in addiction treatment. Repurposing existing drugs in this way offers a potential shortcut around the often lengthy and expensive drug development process, resulting in significant time and cost savings.

NIH invests in specialized resources that support the development of medical and nonmedical treatments for chronic diseases. In response to a congressional mandate, NIH established the Therapeutics for Rare and Neglected Diseases Program (TRND) to bridge the gap between basic research and human testing of new drugs for rare and neglected diseases. TRND is expected to be a highly collaborative effort that will solicit projects from both extramural and intramural investigators for work within the intramural facility. The program expects to test the potential of both novel and repurposed drugs for new therapeutic applications.

Adherence to available medical or behavioral regimens is another critical element in ensuring the successful management of chronic diseases. Adherence to proven therapies has been found to save lives, reduce morbidity, and improve quality of life, but can be challenging, especially over the long term. Adherence can be a special problem for those with comorbidities who often must follow complicated regimens consisting of multiple medications. NIH supports several research programs aimed at improving adherence to treatment regimens for chronic diseases, including both medication and behavioral regimens. For example, NIH funded several initiatives that target different aspects of the clinical care system that play a role in facilitating or hindering adherence: One initiative focused on testing innovative yet practical interventions to improve *patient* adherence to treatment for chronic diseases such as hypertension, coronary heart disease, and asthma; another supported studies evaluating novel strategies to improve *clinician* adherence to guidelines for treatment of heart, lung, or blood diseases; and a third (which is still ongoing) is evaluating clinically feasible interventions to effect changes in *medical care delivery systems* to improve hypertension management and prevent complications in African Americans.

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NIH-supported investigators are conducting clinical research and intervention trials to evaluate the safety and efficacy of treatments for a wide range of chronic diseases. The examples described below represent only a fraction of the research on drugs, surgical techniques, behavioral therapies, and other strategies for the treatment of chronic diseases within the NIH portfolio. Information about these and other NIH-supported clinical trials is available at the clinicaltrials.gov website.

- *Chronic Obstructive Pulmonary Disease (COPD)*: The Long-Term Oxygen Treatment Trial is evaluating the safety and effectiveness of home oxygen therapy for patients with COPD and moderately severe hypoxemia (low blood oxygen levels).
- *Idiopathic Pulmonary Fibrosis (IPF)*: The Idiopathic Pulmonary Fibrosis Clinical Research Network is exploring treatments for patients with newly diagnosed IPF using combinations of existing and relevant drugs given at multiple points in the disease process. The first clinical trial within this network to treat pulmonary hypertension in patients with advanced IPF has been completed. Two additional trials are testing other forms of IPF therapy, including single-agent or combination treatment with corticosteroids, azathioprine, and N-acetylcysteine, as well as oral anticoagulation therapy for fibrosis progression.
- *Obstructive Sleep Apnea (OSA)*: The Apnea Positive Pressure Long-Term Efficacy Study is assessing the role of nasal continuous positive airway pressure (CPAP) in alleviating cognitive impairment associated with OSA. The Impact of CPAP on Functional Outcomes in Milder Obstructive Sleep Apnea study is evaluating the threshold of OSA severity at which CPAP therapy improves sleep-related functional and medical outcomes. The results of both multicenter trials are expected to be released in 2010.
- *Diabetic Cardiovascular Disease*: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to assess whether the rate of major cardiovascular disease events in persons with longstanding type 2 diabetes and who have cardiovascular disease or two or more risk factors for developing it could be reduced by intensive control of blood sugar (glycemia) compared with the current standard of care, intensive control of blood pressure compared with the current standard of care, or treatment of blood lipids with fibrate plus statins compared with treatment with statins alone. In this trial, the intensive group aimed to lower blood sugar levels to be similar to those found in adults without diabetes, whereas the standard group had a target similar to what is achieved, on average, by individuals treated for type 2 diabetes in the United States. The intensive blood glucose management was stopped early due to evidence of higher mortality among people in the intensive group compared with those who received the current standard of care. The blood pressure and lipid components of the trial proceeded as designed.
- *Diabetic Retinopathy*: The collaborative Diabetic Retinopathy Clinical Research Network facilitates multicenter clinical research of diabetic retinopathy and macular edema. Approximately two-thirds of the 117 sites are community-based practices, representing about a third of the U.S. retina specialists in 38 states and involving more than 1,300 health care practitioners. In collaborations with industry, the network compares the effectiveness of surgical, drug, and laser therapies and examines the diagnostic potential of new imaging tools.
- *Type 2 Diabetes*: The Look AHEAD (Action for Health in Diabetes) trial is examining the long-term health effects of an intensive lifestyle intervention designed to achieve and maintain weight loss in overweight or obese adults with type 2 diabetes. Results from the first year of the trial showed that clinically significant weight loss could be achieved through an intensive lifestyle intervention, and that this weight loss was associated with improvements in health-related quality of life, cardiovascular fitness, blood pressure, cholesterol, and blood glucose.
- *Attention Deficit Hyperactivity Disorder (ADHD)*: The Multimodal Treatment Study of Children with ADHD reported that treatment with stimulant medication alone or in combination with psychosocial/behavioral treatment was more effective than behavioral treatments alone or routine community care in reducing the symptoms of diagnosed ADHD in elementary school children. A follow-up study continues to observe long-term outcomes in study participants as they enter adolescence and early adulthood.
- *Functional Gastrointestinal (GI) Disorders*: Several clinical trials are underway to improve the diagnosis and treatment of functional GI disorders. For example, the Functional Dyspepsia Treatment Trial is testing the use of antidepressants for functional dyspepsia (indigestion). Antidepressant therapy also is being tested as a treatment for gastroparesis, the slow movement of food from the stomach to the intestinal tract. A short-term behavioral treatment is being evaluated in patients with irritable bowel syndrome.
- *Asthma*: The NIH Inner-City Asthma Consortium is conducting multiple studies of immune-based therapies to prevent and treat asthma in inner-city children. One ongoing trial is investigating the safety, dosing level, and biologic activity of a potential immunotherapy for cockroach allergen, a major determinant of asthma severity in this population.
- *Liver Diseases*: NIH supports clinical research on multiple liver diseases that affect children and adults. For example, the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network is conducting placebo-controlled trials of potential NASH therapies, including pioglitazone or vitamin E in adult patients and metformin or vitamin E in children. Adult and pediatric Acute Liver Failure Study Groups are evaluating potential therapies to improve survival of patients with acute liver failure due to drugs or other factors.
- *Pelvic Floor Disorders*: The Pelvic Floor Disorders Network investigates new prevention and treatment strategies for pelvic floor disorders, which affect nearly one-quarter of all women in the United States. In one network trial, researchers demonstrated that a two-step surgical procedure, compared to standard practice, could halve the incidence

of urinary incontinence in women with pelvic floor prolapse. Another group of researchers conducted the Program to Reduce Incontinence by Diet and Exercise. This study showed that weight loss could reduce the frequency of urinary incontinence in overweight and obese women.

- *Alcohol Dependence*: NIH is establishing a multicenter network to conduct Phase II trials for treatment of alcohol dependence. Quetiapine and levetiracetam are examples of drugs being tested by the network. In a trial conducted by another group of investigators, alcohol-dependent patients who recently had stopped drinking were given a drug that blocks a brain chemical involved in response to stress. Patients treated with this drug experienced reduced alcohol cravings, improved overall well-being, and reduced blood levels of stress hormones.
- *Obesity*: The Longitudinal Assessment of Bariatric Surgery (LABS) consortium is evaluating the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. A related observational study, Teen-LABS, is collecting data on bariatric surgery in obese adolescents to determine whether surgery is an appropriate treatment option in that age group.
- *Dental Disease*: Three dental practice-based research networks have been launched to train practicing dentists in clinical research and expand the evidence base in dentistry. One area of focus for the networks is testing new treatment strategies for dental caries (tooth decay), which is a common chronic condition in youth.
- *Age-Related Macular Degeneration (AMD) and Cataract*: Following up on the successful multicenter Age-Related Eye Disease Study (AREDS), which showed high-dose antioxidant supplements can slow the progression of AMD, AREDS 2 will test oral supplementation of lutein/zeaxanthin and omega-3 fatty acids for the prevention of AMD and cataract.
- *End-Stage Renal Disease (ESRD)*: Patients being treated with hemodialysis for ESRD (kidney failure) often undergo a procedure to create a site on the body that allows easy, frequent access to blood vessels. Over time, these access sites can become unusable. The Dialysis Access Consortium found that treatment with an anti-clotting drug did not improve long-term usability of fistulas, one type of access site. Separately, the consortium showed that a combination of aspirin and another anti-clotting drug could improve the long-term usability of another access site type, known as a graft. The new Vascular Biology of Hemodialysis Vascular Access Consortium will study the basic mechanisms of vascular access failure, a line of research that could inform future strategies to improve outcomes in ESRD patients.
- *Substance Abuse*: Computer-Based Training for Cognitive Behavioral Therapy is a computer-based training program that focuses on teaching basic coping skills, presenting examples of effective use of coping skills in a number of realistic situations in video form, and providing opportunities for patients to practice and review new skills while receiving substance abuse treatment. This delivery of cognitive behavioral therapy appears to have both short-term and enduring effects in reducing drug use. Such technology increasingly will be harnessed as a low-cost option to provide evidence-based addiction treatments and broaden their availability.

As a public agency, NIH has a particular interest in comparative effectiveness research (CER), which compares two or more treatments for a given condition to determine which treatment is most effective in "real-world" settings.[109] For example, the Acute Renal Failure Trial Network studied patients with acute kidney failure and failure of at least one other organ or a serious infection. Network researchers found no survival benefits from an intensive dialysis regimen compared to conventional dialysis. This finding could spare critically ill patients from unnecessary medical interventions. The Comparison of AMD Treatments Trials (CATT): Lucentis-Avastin Trial is assessing the relative safety and efficacy of two FDA-approved drugs in the treatment of age-related macular degeneration (AMD). One drug, Lucentis™, was specifically approved for AMD treatment and costs around $2,000 per month. A second drug, Avastin®, originally was approved for treatment of colorectal cancer, but its similarity to Lucentis™ has led some clinicians to use Avastin® to treat AMD patients. Because Avastin® costs approximately $100 per month, rigorous evidence that the benefits and risks of Lucentis™ and Avastin® are comparable could result in significant health care cost savings. Additional information regarding NIH's CER-related activities can be found in *Chapter 3: Clinical and Translational Research.*

As a public agency, NIH has a particular interest in comparative effectiveness research, which compares two or more treatments for a given condition to determine which treatment is most effective in "real-world" settings. The Comparison of AMD Treatments Trials: Lucentis-Avastin Trial is assessing the relative safety and efficacy of two FDA-approved drugs in the treatment of age-related macular degeneration.

Comparative effectiveness research can reveal that a one-size-fits-all approach to treating disease is not always appropriate. In some cases, carefully defined subgroups of patients may benefit more—or experience higher risks—from certain treatments than other patients. The BARI 2D trial compared management strategies for patients with stable coronary artery disease and type 2 diabetes. The goal was to determine whether mortality and cardiovascular disease event rates could be reduced by early coronary revascularization and intensive medical therapy compared with intensive medical therapy alone, and by an initial strategy of insulin sensitization compared with provision of insulin to treat hyperglycemia. The trial found that neither early revascularization nor insulin sensitization was superior to the tested alternatives in terms of cardiovascular disease event rates. However, in a subgroup of patients for whom bypass surgery was deemed appropriate, prompt revascularization did reduce the rate of major, nonfatal cardiovascular events.

For many patients with severe organ damage due to chronic disease or injury, the only viable, long-term treatment option is organ transplantation. NIH supports a range of research programs to improve organ transplantation procedures, develop strategies for immune tolerance that could preclude the need for lifelong immunosuppression in transplant patients, and increase the supply of organs for transplantation. The Clinical Trials in Organ Transplantation (CTOT) program was established to improve organ transplantation outcomes by conducting both clinical and mechanistic studies. In one CTOT study, investigators developed a protocol for kidney transplantation and immunosuppressive therapy that allowed 4 out of 5 patients to discontinue all immunosuppressive drugs after 9 to 14 months without rejection of the transplanted kidney. In the area of pediatric liver transplantation, the Childhood Liver Disease Research and Education Network is exploring treatment options for children with liver diseases or who have undergone liver transplantation. Another network is planning a study of immunosuppression minimization in children after liver transplantation. Another major effort, the Immune Tolerance Network, is developing new approaches to establishing immune tolerance in patients who have undergone kidney, liver, or pancreatic islet transplantation. Importantly, immune tolerance strategies for transplantation could have applications in the treatment of asthma, allergies, and autoimmune diseases, including type 1 diabetes, multiple sclerosis, and lupus erythematosus.

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Organ transplantation has been a life-changing—oftentimes, life-saving—procedure for countless patients with chronic disease. However, many patients who could potentially benefit from a transplant are not able to receive one due to shortages of suitable organs for transplantation. The Cornea Donor Study demonstrated that corneal transplants using tissue from 66- to 75-year-old donors have success rates similar to transplants using tissue from 12- to 65-year-old donors. Because corneal tissue from donors ages 65 and older traditionally has been rejected for transplantation purposes, this result has the potential to expand the pool of cornea donors and ensure an adequate supply of tissue for transplantation.

The use of complementary and alternative medicine (CAM) is common among the American public. The 2007 National Health Interview Survey found that 38 percent of adults and 12 percent of children use some form of CAM, such as nonvitamin/nonmineral natural products, deep breathing, meditation, massage therapy, and yoga. NIH supports a substantial research effort to provide evidence-based evaluation of the safety and efficacy of CAM practices. For example, the Glucosamine/Chondroitin Arthritis Intervention Trial assessed the use of these dietary supplements to treat pain and reduce structural damage associated with knee osteoarthritis. Researchers discovered that combined glucosamine/chondroitin sulfate treatment did not provide significant pain relief among study participants overall; however, a subgroup of subjects with moderate to severe pain did experience significant relief. Treatment with the supplements alone or in combination did not improve loss of cartilage in osteoarthritis of the knee compared to a placebo.

Addressing Pain and Palliative Care in Chronic Diseases

Many chronic diseases are associated with pain that can be chronic and severe. Pain often is difficult to treat and can significantly erode patients' quality of life. NIH supports a spectrum of pain research that includes basic science to understand the mechanisms of pain and pain relief, as well as clinical research to evaluate pharmacological, surgical, and alternative strategies for pain management. For example, researchers have identified two enzymes of the matrix metalloprotease family that are involved in the early development and persistence of chronic neuropathic pain due to nerve injury. Other researchers have discovered ways to selectively activate the cannabinoid system to provide pain relief without the effects on mental function and abuse potential that are common to opioid-based analgesics. Both findings will inform ongoing research to develop safe, effective, and nonaddictive drugs for pain relief. At the clinical level, NIH-supported researchers are testing the effectiveness of nonpharmacological approaches for the treatment of chronic low back pain. The Spine Patient Outcomes Research Trial (SPORT) showed that surgery is more effective than nonoperative treatments, such as medications and physical therapy, for the most common causes of chronic, severe low back pain.

Impressive progress has been made in recent years in understanding the mechanisms of pain and developing treatments, especially for common conditions such as low back pain. However, little is known about the biological mechanisms of pain in rare conditions, such as sickle cell disease, that are associated with lifelong, often severe pain. NIH launched an initiative, Exploratory Studies in the Neurobiology of Pain in Sickle Cell Disease, to foster basic and translational research on the unique aspects of pain in this disease. The initiative encourages multidisciplinary approaches that bring together experts in relevant fields, including neurobiology, hematology, pharmacology, and psychology.

Some patients with chronic pain turn to alternative therapies. For example, in a recent study, investigators compared the efficacy of acupuncture with either standardized or customized needle placement, "simulated acupuncture" without skin puncture, and conventional care for chronic low-back pain. After 8 weeks, participants in all 3 acupuncture groups improved their dysfunction scores significantly more than the group receiving usual care. Notably, simulated acupuncture was as effective as acupuncture with either standardized or customized needle placements, raising intriguing questions about the mechanisms by which acupuncture relieves pain.

Palliative care, which includes pain management, focuses on alleviating disease symptoms and improving patients' quality of life. Optimizing end-of-life care is an important topic within the field of palliative care research, particularly with respect to understanding the needs of dying children with chronic diseases and their families. Researchers also are studying the many cultural, spiritual, age-related, and disease-specific factors that affect the end of life. Because each person's experience at the end of life is unique, NIH has developed an initiative to support research on interventions for end-of-life and palliative care that can be applied in a variety of settings, illnesses, and cultural contexts.

A Commitment to Global Health

Chronic diseases take a substantial toll on public health and well-being across the globe. According to the World Health Organization, chronic diseases account for 60 percent of deaths worldwide; fully 80 percent of chronic disease-related deaths occur in low- and middle-income countries (LMICs). The number of deaths from chronic disease in these countries is double the number of deaths resulting from infectious disease (including HIV/AIDS, malaria, and tuberculosis), maternal and perinatal conditions, and nutritional deficiencies combined. Furthermore, the burden of chronic disease in the developing world is projected to rise dramatically in the coming decades. This increasing burden can be attributed to a number of factors, including longer average lifespan, tobacco use, decreasing physical activity, and increasing consumption of unhealthy foods.[110]

NIH is committed to addressing this global health problem with a variety of approaches that include support for international research projects and initiatives to build research capacity in LMICs. For example, the NIH-supported International Tobacco and Health Research and Capacity Building Program demonstrated that smoking was associated

with 6- and 8-year reductions in median survival for men and women in India, respectively. This project provided important data on the smoking epidemic in India that can inform public health efforts to educate people in that country on the effects of smoking. In June 2009, NIH joined the United Health Chronic Disease Initiative and established a network of 11 Collaborating Centers of Excellence in LMICs to build sustainable programs to combat chronic cardiovascular and lung diseases. Each center pairs a research institution in a developing country with at least one academic institution in a developed country.

Future NIH research directions in global health will be informed by a 2009 report of the Institute of Medicine (IOM), *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sector*.[111] This report, which updates a 1997 IOM report, lays out arguments for public and private investment in global health and presents key recommendations to guide such investments. Notably, the report calls for additional resources and the adoption of clear health goals to guide the allocation of funds targeted at the reduction of the burden of noncommunicable disease.

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Addressing the steady increase in chronic noncommunicable diseases around the world requires a well-trained research workforce with the expertise to study these diseases and their treatments in low- and middle-income countries (LMICs). The new Millennium Promise Awards: Noncommunicable Chronic Diseases Research Training Program supports research training for scientists in LMICs with a focus on cancer, cerebrovascular disease, lung disease, and obesity. The program encompasses a broad range of research, from understanding genetic and lifestyle factors in the development of chronic diseases to the translation of research outcomes into public health programs and policies that are culturally relevant and sensitive.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Understanding Fundamental Mechanisms of Organ Health and Disease

New Therapeutic Target for Macular Degeneration and Diabetic Retinopathy Discovered: Neovascularization is the term used to describe the growth of abnormal new blood vessels. In some diseases, such as age-related macular degeneration or diabetic retinopathy, neovascularization mistakenly activates and becomes a major pathologic feature. The abnormal vessels leak fluid and serum, which damages the light-sensitive photoreceptor cells in the retina, causing severe and irreversible vision loss. NIH-sponsored research is focused on understanding the pathways that inhibit and promote neovascularization. Previous studies have established that a protein called vascular endothelial growth factor (VEGF) spurs neovascularization, and several therapies have been developed to prevent the abnormal activation of VEGF. A recent

NIH-supported study reported the discovery of Roundabout4 (Robo4), a protein that stabilizes the existing vasculature and prevents neovascularization by inhibiting VEGF activity. Robo4 is among a family of Roundabout proteins that previously were found to act as guidance receptors for developing neurons in the nervous system. That Robo4 plays a different and central role in controlling neovascularization represents a breakthrough that may lead to new treatments to prevent or delay the sight-threatening consequences of vascular eye diseases.

- → Jones CA, et al. *Nat Med* 2008;14(4):448-53. PMID: 18345009.
- → For more information, see http://www.nature.com/nm/journal/v14/n4/full/nm1742.html
- → This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- → (E) (**NEI**)

Neurobiology of Appetite Control: NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. For example, the sight of food has been found to induce different responses in the brains of patients following weight loss; these differences are due to changes in levels of the hormone leptin. Researchers also discovered that rats susceptible to becoming obese from a high-calorie diet have fewer neural connections in the brain in the hypothalamus (the part of the brain that has a key role in weight regulation) compared to normal rats. Additionally, a factor secreted by the small intestine in response to dietary fat intake has been found to enter the brain and suppress appetite in rats. More recently, six new genetic regions associated with obesity were identified and found to be in or near genes expressed in the brain. To highlight further the connection between brain function and obesity, a trans-NIH workshop on neuroimaging in obesity research was held to share data and experiences with functional neuroimaging approaches to study brain involvement in various aspects of obesity such as weight gain and loss, and the neurotransmitters and brain structures associated with energy balance, hunger, and decision-making. A recent funding opportunity announcement was issued to foster new research using neuroimaging approaches to enhance understanding of food intake and energy expenditure in the context of obesity. This research has implications for new therapies for obesity.

- → Rosenbaum M, et al. *J Clin Invest* 2008;118(7):2583-91. PMID: 18568078. PMCID: PMC2430499.
  Bouret SG, et al. *Cell Metab* 2008;7:7(2):179-85.PMID: 18249177. PMCID: PMC2442478.
  Gillum MP, et al. *Cell* 2008;135(5):813-24.PMID: 19041747. PMCID: PMC2643061.
  Willer CJ, et al. *Nat Genet* 2009;41(1):25-34. PMID: 19079261. PMCID: PMC2695662.
- → For more information, see http://www3.niddk.nih.gov/fund/other/neuroimaging2008/
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/rfa-dk-08-009.html
- → This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
- → (E) (**NIDDK**)

Genes Involved in the Regulation of Sensitivity to Alcohol: Low doses of alcohol are stimulating in both humans and animals while higher doses have sedating effects. Sensitivity to alcohol, however, varies across individuals and low sensitivity to alcohol is a risk factor for the development of alcohol dependence in humans. Research with individuals who have a high family history of alcoholism seeks to understand how low response to alcohol contributes to dependence and how it can be used to predict risk for future alcohol problems. Research with animals is useful in identifying the mechanism(s) underlying the level of sensitivity to alcohol. Recently, a study with fruit flies implicated the Epidermal Growth Factor Receptor (EGFR) signaling pathway in regulating sensitivity to alcohol. Importantly, FDA-approved medications that inhibit EGFR increase alcohol sensitivity in mice and decrease alcohol intake in rats, suggesting that these drugs may offer therapeutic opportunities for treatment of alcohol use disorders in humans.

- → Corl AB, et al. *Cell* 2009;137(5):949-60. PMID: 19464045.
  Trim RS, et al. *Alcohol Clin Exp Res* 2009;33(9):1562-70. PMID: 19485971.
- → This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
- → (E) (**NIAAA**)

Research and Treatment of Drug-Induced Liver Disease: Drug-induced liver toxicity is increasing in the United States and has serious consequences for individuals and society. Alcohol- and diet-induced fatty liver are major causes of morbidity, and knowledge of the mechanisms involved is incomplete. NIH has implemented major research initiatives to study basic liver function, to determine how alcohol and drug abuse cause liver injury and disease, and to develop new medications for treatment of liver disease. For example, NIH researchers are beginning to shed light on the molecular mechanisms of fatty liver, demonstrating that specific chemical messengers (known as endocannabinoids) and their receptors contribute to both diet- and alcohol-induced fatty liver and its metabolic consequences. These and related studies suggest that endocannabinoid receptors could be targeted selectively in drug development for treatment of fatty liver and impaired blood sugar regulation. NIH also has implemented the Drug-Induced Liver Injury Network (DILIN). This network facilitates research on liver toxicity due to prescription drugs or complementary and alternative medicines. Current studies are developing better tools for diagnosing, and ultimately preventing, drug-induced liver injury, as well as enhancing knowledge of liver disease processes. The network has evolved into a resource on drug-induced liver toxicity for the national clinical community and the public.

→ Jeong WI, et al. *Cell Metab* 2008;7(3):227-35. PMID: 18316028.
Osei-Hyiaman D, et al. *Clin Invest* 2008;118(9):3160-9. PMID: 18677409. PMCID: PMC2491458.
→ For more information, see https://dilin.dcri.duke.edu/
→ (E/I) (**NIAAA**, NIDDK)

Beneficial and Harmful Actions of Alcohol on the Heart Involve Alcohol-Metabolizing Enzyme: Cardiac ischemia, damage to heart muscle caused by reduced or blocked blood flow, affects nearly 1 million people in the United States annually and is the leading cause of death in developed countries. The beneficial effects of moderate levels of alcohol consumption on the heart have been well-documented, and may significantly protect the heart against ischemic injury. Protection involves a preconditioning-like mechanism through activation of the molecule protein kinase C epsilon (PKCe), or prior exposure to certain chemicals such as ethanol, but the underlying molecular targets of this protection remain obscure. Recently researchers showed that in response to ethanol treatment or PKCe activation, the activity and phosphorylation of aldehyde dehydrogenase-2 (ALDH2), the main enzyme that mediates elimination of alcohol from the body, increased and correlated with cardioprotection in rat hearts. A related study showed PKCe moves to the mitochondria where it binds to ALDH2 and, through multiple pathways, significantly reduced ischemic injury. A screen for small molecules that could activate ALDH2 recently identified one with therapeutic potential for individuals subject to cardiac ischemia, including during coronary bypass surgery.

In contrast to the cardioprotective effects observed with moderate alcohol consumption, chronic heavy consumption can cause alcoholic cardiomyopathy (disease of the heart muscle) with hallmark features of abnormal heart enlargement and compromised contractility of heart muscle. Current investigations link acetaldehyde toxicity (a by-product of alcohol metabolism) to alcoholic cardiomyopathy and demonstrate that increased levels of ALDH2 can reduce these effects.

→ Churchill EN, et al. *J Mol Cell Cardiol* 2009;46(2):278-84. PMID: 18983847. PMCID: PMC2675554.
Doser TA, et al. *Circulation* 2009;119(14):1941-9. PMID: 19332462. PMCID: PMC2740924.
Chen CH, et al. *Science* 2008;321(5895):1493-5. PMID: 18787169. PMCID: PMC2741612.
→ (E) (**NIAAA**)

Scientists Demonstrate Hematopoietic Stem Cells' Role in Forming the Stem Cell Niche: Stem cells are important in all multicellular organisms because they have the ability to develop into different kinds of specialized cells. Outside of the organism, researchers can grow stem cells in specific cultures and observe the development of specialized cells. Blood-forming stem cells, known as hematopoietic stem cells (HSCs), are controlled by the hematopoietic stem cell niche, which is located in the bone marrow. Bone-forming cells called osteoblasts are known to play a central role in establishing the HSC niche; however, it is unclear whether HSCs in turn control the differentiation of stem cells that become osteoblasts. Although such interactions in the niche have been proposed, at present there is insufficient direct experimental evidence to

define the relationship between HSCs and osteoblast formation. In this work, a group of investigators addressed the role of HSCs in the differentiation of osteoblasts. Using mice, they co-cultured HSCs with stem cells that become osteoblasts, and demonstrated that HSCs can indeed affect the differentiation of cells into osteoblasts. Further, the investigators found that the specialization or differentiation into osteoblasts could be influenced by the age and physical condition of the mice. These findings suggest that HSCs may serve as an important therapeutic target for controlling bone formation and repair. In particular, it should be possible to develop therapeutic agents that specifically target HSCs for treatment of a variety of bone defect such as osteoporosis, nonhealing bone and tooth defects, and congenital bone abnormalities.

→ Jung Y, et al. *Stem Cells* 2008;26(8):2042-51. PMID: 18499897.
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDCR**)

Obesity, Inflammation, and Fat Cell Biology: NIH supports diverse research on fat (adipose) tissue, including studies that examine the relationship between obesity and inflammation in white adipose tissue, as well as research on another type of fat tissue, brown fat. In obese patients, lipid laden white adipose tissue secretes a number of proinflammatory molecules such as TNF-alpha (as well as other types of signaling molecules associated with insulin resistance). Chronic low-grade tissue inflammation observed in obese individuals has been linked to type 2 diabetes and cardiovascular disease risk. An NIH-funded, multicenter research study called Targeting INflammation using SALsalate for Type-2 Diabetes (TINSAL-T2D) has been initiated to determine whether salsalate, an inexpensive anti-inflammatory drug, could be a new treatment option for patients with type 2 diabetes. A different avenue of research led to the surprising discovery of metabolically active brown adipose tissue in adult humans. While white fat cells store fat, brown fat cells burn fat to generate heat, and were once thought to exist only in infants. Research on brown fat in adult humans, as well as studies in animal models, may lead to novel strategies for obesity therapy.

→ Cypess AM, et al. *N Engl J Med* 2009;360(15):1509-17. PMID: 19357406. PMCID: PMC1986615.
Tseng YH, et al. *Nature* 2008;454(7207):1000-4.PMID: 18719589. PMCID: PMC2745972.
Seale P, et al. *Nature* 2008;454(7207):961-7. PMID: 18719582. PMCID: PMC2583329.
→ For more information, see http://tinsalt2d.org/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**)

Atopic Dermatitis: Investigations in the molecular pathways leading to atopic dermatitis, the most common form of eczema, have identified defects in the skin's protective mechanisms against pathogenic microbes and inflammation-associated immune responses. Researchers have learned that the skin of atopic dermatitis patients is heavily colonized by bacteria, such as *Staphylococcus aureus*, and they have frequent skin infections. Atopic dermatitis patients also have high levels of the messenger molecules, Th2 cytokines, in their skin, which are involved in immune function. These concentrations in atopic dermatitis patient skin have been found to inhibit the release of an antimicrobial protein, human beta-defensin 3, that can kill *S. aureus*. As well, breakdown of skin's barrier function may be a contributor to the disease. The failure of skin integrity allows environmental factors to trigger inflammatory signals that provoke asthma symptoms in a mouse model, and may provide an explanation for the occurrence of asthma in 50 percent of pediatric atopic dermatitis cases. In addition, molecular pathways, which are triggered by bacterial infections in the skin and drive inflammation in atopic dermatitis, have been identified. These genetic and biochemical studies provide important therapeutic targets for the development of treatments to interrupt aberrant disease mechanisms.

→ He R, et al. *Proc Natl Acad Sci U S A* 2007;104(40):15817-22. PMID: 17893340. PMCID: PMC2000444.
Kisich KO, et al. *J Allergy Clin Immunol* 2008;122(1):62-8. PMID: 18538383.
He R, et al. *Proc Natl Acad Sci U S A* 2008;105(33):11875-80. PMID: 18711124. PMCID: PMC2575291.
Jin H, et al. *J Clin Invest* 2009;119(1):47-60. PMID: 19075398. PMCID: PMC2613448.
→ (E) (**NIAMS**)

Metabolic Network Model of a Human Oral Pathogen: The bacterium *Porphyromonas gingivalis* causes severe, chronic periodontal disease. Recently NIH-supported researchers constructed a complex metabolic network map for *P. gingivalis* with which to model the metabolic properties of all genomically identified components of the system. The scientists used a technique known as flux-balance analysis (FBA) to construct the model, which consisted of 679 metabolic reactions involving 564 metabolites. There was significant correlation between the model's predictions and the bacterium's experimentally observed metabolism. The true power of this model became apparent when "virtual knockouts" were employed to predict the effect of the loss of certain genes or metabolic pathways on growth rate, and the model very effectively predicted disturbances affecting biosynthesis of large molecules known as lipopolysaccharides. This is the first description of a model of this type for an oral periodontal pathogen. Still in their infancy, metabolic network models are a logical extension of genome sequence data. They can provide the ability to perform virtual metabolic modeling of organisms with limited or no in vivo experimental histories. These models also could be applied to highly interdependent mixed microbial communities, including the oral microbiome, ultimately resulting in new biomedical applications. Such modeling greatly increases opportunities to discover new antibacterial drug targets. These studies provide new molecular targets for therapeutic drugs; they also can suggest the molecular mechanisms for virulence, intracellular persistence and survival, and ability of the bacteria to survive stresses from the (in this case, human) host defense mechanisms.

→ Mazumdar V, et al. *J Bacteriol* 2009;191(1):74-90. PMID: 18931137. PMCID: PMC2612419.
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NIDCR**)

Challenge Program in Integrative Research: Mechanisms of Susceptibility to Oxidative-Stress Disease: This project is an interdisciplinary, collaborative effort to combine the use of simple eukaryotic systems, mouse models, genetic polymorphisms, genomics, clinical research, and patient samples to investigate the mechanisms of susceptibility to the development of oxidative stress-induced disease. The initial phase of the program is focused on bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP), chronic diseases associated with very low birth weight infants. This program consists of three interactive projects: (1) positional cloning of BPD/ROP susceptibility genes in inbred mice; (2) investigating the role of mitochondrial reactive oxygen species in hyperoxia-induced tissue injury; and (3) searching for oxidant susceptibility genes and neonatal diseases in prospective case-parent triad cohorts. Together this group will identify stress response networks, develop and validate early biomarkers of disease, and identify candidate genes and genetic polymorphisms that influence susceptibility to oxidative stress. This program has established a highly collaborative research team uniting bench science with clinical research and patient outcomes. The long-term goal of this program is to understand the role of specific genes that increase human susceptibility to oxidant stress-induced diseases. Thus, this team has the potential to affect a large number of environmentally induced diseases associated with inflammation and reactive oxygen species, including asthma, atherosclerosis, cancer, cardiovascular disorders, and neurodegenerative diseases.

→ This example also appears in Chapter 3: *Genomics* and Chapter 3: *Clinical and Translational Research*
→ (I) (**NIEHS**)

New Pig Model of Cystic Fibrosis: An NIH-supported research team has generated pigs that lack the CFTR gene, which is responsible for the disease, or possess one of its common mutations. The newborn piglets without CFTR have presentations at birth and shortly thereafter that are similar to those seen in human infants with cystic fibrosis (CF), including typical abnormalities in the intestines, pancreas, and liver. As with human infants, the piglets lacking CFTR do not exhibit obvious lung abnormalities at birth. However, they have the typical ion transport properties of CF airway epithelia and are expected to develop the progressive lung changes over time seen in humans. The development of this pig model represents a major breakthrough in research on cystic fibrosis. In addition to offering unprecedented opportunities to understand how the respiratory disease develops during early childhood, it will allow testing of new preventive and

therapeutic strategies. In 2008 and 2009, NIH funded two multidisciplinary program project grants to advance study of this new large-animal model for CF. The research will advance understanding of the pathogenesis and pathophysiology of airway disease and spur development of gene therapy and other pharmacologic approaches for CF lung disease.

→ Rogers CS, et al. *Science* 2008;321(5897):1837-1841. PMID: 18818360. PMCID: PMC2570747.
→ (E) (**NHLBI**, NIAID, NIDDK)

Trans-NIH Working Group for Research on Chronic Fatigue Syndrome (CFS): The multisystemic nature of CFS requires multidisciplinary and interdisciplinary efforts that cut across the missions of all NIH ICs. NIH coordinates CFS research through a Trans-NIH Working Group for Research of Chronic Fatigue Syndrome (CFSWG). The CFSWG is guided by an action plan centered on enhancing the status of CFS research at NIH and among the external and intramural scientific communities. NIH funded a diverse range of projects that hold promise for developing biological markers and potential treatments for CFS and issued new funding opportunities. The first annual meeting of principal investigators whose research projects are specific to understanding the relationship of neuroimmune mechanisms and CFS was held to foster an interdisciplinary collaboration to accelerate research in this area of science through a consortium. Investigators participated in creative team-building that was focused on integrating their research with the hypothesis that an original infectious insult might affect and perpetuate the many symptoms of CFS. Planning is underway for a follow-up workshop that will be expanded to include other CFS researchers.

→ For more information, see http://orwh.od.nih.gov/cfs.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-246.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-247.html
→ (E) (**ORWH**, NCCAM, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIDCR, NIEHS, NIMH, NINDS, NINR, OBSSR, ODP/ODS)

Brain Matures a Few Years Late in ADHD: NIH-supported research on brain development in children with attention-deficit/hyperactivity disorder (ADHD) showed a normal pattern of brain development, but with a striking delay in cortical maturation. Between ages 5 and 15, the maturation of the prefrontal cortex was found to be delayed by roughly 3 years in children with ADHD compared to age-matched children without the disorder. Current studies now are exploring the effects of treatment on the rate of cortical maturation.

→ Shaw P, et al. *Proc Nat Acad Sci U S A* 2007;104(49):19649-54. PMID: 18024590. PMCID: PMC2148343.
→ For more information, see http://www.nimh.nih.gov/science-news/2007/brain-matures-a-few-years-late-in-adhd-but-follows-normal-pattern.shtml
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (I) (**NIMH**)

Detecting and Diagnosing Chronic Disease

Screening and Brief Intervention: Given the pervasiveness of high-risk drinking and the high prevalence of alcohol dependence occurring among young adults, efforts to alter drinking trajectories at this stage have life-changing potential and significantly can reduce the burden of illness resulting from alcohol-related problems. NIH actively is engaging the medical community to increase the number of primary care and mental health clinicians who advise, counsel, and treat their patients regarding harmful patterns of alcohol use, including alcohol dependence. NIH continues to promote and disseminate *The Clinician's Guide: Helping Patients Who Drink Too Much* and the associated online training modules. For individuals with milder forms of dependence, who are much less likely to seek any form of alcohol treatment, the integration of alcohol screening and brief intervention into primary care is a cost-effective way to ensure that they receive appropriate care early in the course of their disease. NIH now is exploring other venues for delivery of screening and brief

intervention such as emergency departments and college student health centers. Other research objectives are to test strategies to improve screening methods to identify youth with or at high risk for alcohol-related problems, and to test the effectiveness of novel methods to prevent or delay the initiation of alcohol use and decrease the risk for development of alcohol use disorders among youth. Several of these studies examined the effectiveness of interventions that involve parents/families. Other studies focus on what factors increase use and effectiveness of alcohol screening and brief intervention in various settings.

→ Schaus J, et al. *J Stud Alcohol Drugs* 2009;16:131-141. PMID: 19538921. PMCID: PMC2701092.
Schaus J, et al. *J Stud Alcohol Drugs* 2009;16:34-44. PMID: 19538911. PMCID: PMC2701091.
Nilsen P, et al. *J Subst Abuse Treat* 2008;35(2):184-201. PMID: 18083321.
Academic ED SBIRT Research Collaborative. *Ann Emerg Med* 2007;50(6):699-710.e6. PMID: 17870206.
Chun TH, et al. *Pediatr Emerg Care* 2008;24(10):668-72. PMID: 19242135.
Sindelar-Manning H, et al. *Pediatr Emerg Care* 2008;24(7):457-61. PMID: 18580703.
Roudsari B, et al. *Ann Emerg Med* 2009;54(2):285-93. PMID: 19250705. PMCID: PMC2745201.
→ For more information, see http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm
→ For more information, see http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/CME_CE.htm
→ (E) (**NIAAA**)

Reaching Out to Teens and Health Care Professionals: In the spring of 2009, NIDA unveiled NIDAMED, its first comprehensive physicians' outreach initiative. NIDAMED gives medical professionals a variety of information, including tools and resources, to help in screening patients for tobacco, alcohol, and illicit and nonmedical prescription drug use. The NIDAMED website contains links to numerous resources for health care professionals: an online screening tool titled NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NM ASSIST); two guides for clinicians (quick reference and a comprehensive resource guide); a number of key NIDA publications, such as the *Principles of Drug Abuse Treatment: A Research-Based Guide*, *The Science of Addiction*, *a Commonly Abused Drugs Chart*, and a postcard that encourages patients to "Tell Your Doctor About All the Drugs You Use." The NIDAMED initiative stresses the importance of the patient-doctor relationship in identifying and intervening early in patients' drug use behaviors before they evolve into life-threatening conditions. NIH is planning to hold its third annual Drug Facts Chat Day in November 2009. These events let students and teachers in classrooms across the United States ask questions of the Nation's top experts in the field of drug abuse and addiction. NIH staff will gather in a computer lab on the event day and will respond to submitted questions in real time. Chat Day events have proven to be a resounding success. The inaugural event elicited more than 35,000 questions.

→ For more information, see http://www.nida.nih.gov/nidamed
→ For more information, see http://www.nida.nih.gov/scienceofaddiction
→ For more information, see http://www.drugabuse.gov/chat
→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (E) (**NIDA**)

A New Imaging Device for Early Detection of Cataract: A transparent ocular lens is essential to vision. Cataract (clouding of the lens) remains the primary cause of blindness in the world today. Age-related cataract, the most common type of cataract, is caused by abnormal aggregation of lens proteins that clouds the lens. In the last few years, it has been established that a particular lens protein, alpha crystallin, prevents other lens proteins from aggregating and probably plays a major role in preventing cataract formation. Humans are born with a fixed amount of alpha crystallin, so age-related cataracts occur when the supply is depleted. Researchers at NIH and NASA collaborated to develop a new imaging device that allows clinicians to detect and quantify the amount of unbound alpha crystallin protein in a patient's eye. The device uses dynamic light scattering to measure the amount of alpha crystallin remaining in the lens. This may lead to a better understanding of the early stages of protein aggregation before cataracts form that impinge on vision. Early detection of lens protein disruption may provide clues to preventive treatments that could delay the need for cataract surgery.

→ Datiles MB, et al. *Arch Ophthalmol* 2008;126(12):1687-93. PMID: 19064850. PMCID: PMC2600622.
→ For more information, see http://archopht.ama-assn.org/cgi/content/full/126/12/1687
→ This example also appears in Chapter 3: *Technology Development*
→ (I) (**NEI**)

Feeling Organs with Imaging: MRI is known for providing exquisite anatomical images of internal organs. Using a new technique that involves imaging while pushing on an organ with sound waves, researchers are able to feel the stiffness of internal organs. Because tumors often are more stiff than normal tissue (think, for example, of feeling for a "lump" of stiffer tissue in the breast), this technique may provide important diagnostic information about disease. Initially, this technique is being used to examine the stiffness of liver and potentially provide an alternative to liver biopsy for the 170 million individuals worldwide who live with chronic hepatitis C, a major cause of liver disease.

→ Venkatesh SK, et al. *AJR Am J Roentgenol* 2008;190:1534-40. PMID: 18492904.
Yin M, et al. *Magn Reson Med* 2007;58:346-53. PMID: 17654577.
Yin M, et al. *Clin Gastroenterol Hepatol* 2007;5:1207-13. PMID: 17916548. PMCID: PMC2276978.
Kruse SA, et al. *Neuroimage* 2008;39:231-7. PMID: 17913514. PMCID: PMC2387120.
→ For more information, see http://www.nibib.nih.gov/HealthEdu/eAdvances/28Aug08
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIBIB**)

NIH Undiagnosed Diseases Program (UDP): In May 2008, NIH launched a program to evaluate patients with disorders that have evaded a diagnosis. Often patients seek help from multiple physicians and other health care providers over many years without receiving a diagnosis. Using a unique combination of 35 NIH scientific and medical specialty experts, the UDP pursues three goals: To help patients with unknown disorders reach an accurate diagnosis, to discover new diseases that provide insight into human biology, and to reestablish the NIH CC as the referral Center for mystery diseases. In its first year, the UDP received more than 2,000 inquiries, with approximately half of them of neurological origin, and 100 of them pediatric. Of the 2,000 inquiries in the first year, 850 were followed up with submission of medical records; 450 of the applications to participate in the program were deemed inappropriate; and 158 cases were accepted into the program by 10 Institutes and Centers. The program is trans-NIH in scope. Senior attending physicians with many different medical specialties from NIH research Centers and Institutes contribute the expertise needed to achieve the goals of this clinical research program. Any longstanding medical condition that eludes diagnosis by a referring physician can be considered undiagnosed and may be of clinical interest.

→ For more information, see http://rarediseases.info.nih.gov/Resources.aspx?PageID=31
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**ODP/ORDR, CC, NHGRI**, NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIMH, NINDS, NINR)

Primary Immune Deficiency Diseases: Primary immune deficiency diseases (PIDDs) are caused by inherited defects in specific cells of the immune system. Individuals with PIDDs generally have an increased susceptibility to infections and may have other medical problems that include autoimmune diseases, deteriorating lung function, tumors, and failure to thrive. Approximately 500,000 people in the United States are diagnosed with PIDDs, many of whom are children; many more individuals with PIDDs likely are undiagnosed. The NIH Primary Immune Deficiency (PID) Clinic, established in 2007, provides comprehensive consultations for individuals 6 months and older who have known or suspected PIDDs. Once clinicians determine that a person might benefit from coming to the NIH PID Clinic, he or she will be invited for a thorough examination and diagnostic work-up. After examination, PID Clinic patients and their referring physicians will be given a detailed list of treatment recommendations. NIH clinicians also will follow-up with referring physicians to check on a person's progress and, as needed, make additional recommendations. In a notable science advance, 11 PID Clinic patients with previously unidentified immune diseases obtained a more accurate disease diagnosis. While the patients received care for their symptoms—including persistent skin infections, acute allergies, and cancer—investigators

observed that they all had a mutation in the same gene, DOCK8, which could account for their health problems. Although further study is required to determine if DOCK8 mutations occur in others with similar symptoms, DOCK8 immunodeficiency syndrome may be a new PIDD. Identifying a cause for the disease has provided comfort to some of those diagnosed who had battled an unknown immune disease for years.

→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/DOCK8.htm
→ (I) (**NIAID**)

Identifying Risk and Preventing Chronic Disease

Transdisciplinary Tobacco Use Research Centers (TTURCs)—Alcohol Use and Smoking: Multiple Institutes at NIH are co-funding seven collaborative, transdisciplinary centers to identify familial, early childhood, and lifetime psychosocial pathways related to smoking initiation, use, cessation, and patterns of dependence. Research on genetics of addiction, physiological biomarkers, and the use of advanced imaging techniques can lead to individualized and community approaches for tobacco prevention and treatment. This model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships. Some recent highlights include: For smokers quitting while taking the prescription drug bupropion, the risk of smoking relapse was associated primarily with heavy, rather than with moderate drinking. Interactions between brain pathways activated by nicotine and alcohol may increase the likelihood of drinking in humans who simultaneously smoke and drink, suggesting that drugs that block nicotinic receptors also may help to reduce drinking. Varenicline, an agonist of certain nicotinic acetylcholine receptors, is a smoking cessation medication that has been shown in preclinical research to reduce alcohol drinking. Researchers are testing varenicline in preclinical models of ethanol drinking to determine which nicotinic receptor subtypes are most important. Recently, they found that varenicline reduces alcohol self-administration in heavy-drinking smokers.

→ For more information, see http://dccps.nci.nih.gov/tcrb/tturc
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIAAA**, NCI, NIDA)

Diabetes and Pesticide Exposure/the Agricultural Health Study: Exposure to certain pesticides increased the risk of diabetes in licensed applicators, according to researchers from NIH. The investigation of applicators enrolled in the Agricultural Health Study is the largest study to date to evaluate potential effects of pesticides on diabetes incidence in adults. Because previous studies using data from the National Health and Nutrition Examination Survey (NHANES) found associations of diabetes with serum levels of persistent organic pollutants, the researchers wanted to know if there was a similar association between diabetes and lifetime exposure to pesticides. Therefore, they evaluated applicators who reported diabetes for the first time in 5-year follow-up telephone interviews, conducted between 1999 and 2003. Previously, applicators had described use of 50 different pesticides, providing information on 2 primary measures: ever use and cumulative lifetime days of use. Of 50 pesticides evaluated, 7 were associated with an increased incidence of diabetes using both exposure measures. Three of these were organochlorine insecticides (aldrin, chlordane, heptachlor), 2 were organophosphate insecticides (trichlorfon, dichlorvos), and 2 were herbicides (alachlor, cyanazine). The strongest association was with trichlorfon: Applicators who had used the chemical on more than 10 days in their lifetime had a 2.5-fold increase in risk. Pesticide applicators who reported exposure to these pesticides showed an increased risk of diabetes independent of age, state of residence, and body mass index. The increasing burden of diabetes in populations worldwide warrants an improved understanding of the possible relation of diabetes risk to long-term, low levels of pesticide exposure.

→ Montgomery MP, et al. *Amer J Epidemiol* 2008;167:1235-46. PMID: 18343878.
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E/I) (**NIEHS**, NCI)

Epidemiologic Studies of Osteoporosis: NIH supports several prospective cohort studies, including the Study of Osteoporotic Fractures (SOF) in women and Mr. OS, a study of osteoporosis and other age-related diseases in men. The studies, which have been underway since 1986 and 1999, respectively, identified characteristics associated with fracture risk in older Americans. Assessing risk is important because the devastating consequences of low bone mass can be prevented. For example, simple changes to a person's home (e.g., adding more lights, removing clutter) can prevent falls. A balanced diet and modest exercise build bone strength, and medications can slow disease progression. SOF, Mr. OS, and other studies are providing information about osteoporosis diagnosis, treatment, and prevention. SOF and Mr. OS reinforced a notion, outlined in the Surgeon General's 2004 report on Bone Health and Osteoporosis, that older people who have a fracture should be tested for osteoporosis—even if the fracture occurred because of a traumatic injury (e.g., a fall off a ladder or an auto accident) that could hurt a healthy young person. Mr. OS is generating data that the U.S. Preventive Services Task Force can incorporate into guidance on using bone mineral density to assess fracture risk. Scientists using data from the Framingham Osteoporosis Study recently reported that men and women who consumed the most vitamin C had fewer hip fractures than those who consumed less vitamin C—a finding that may have implications for the recommended intakes established for vitamin C. Women's Health Initiative investigators demonstrated that low blood levels of vitamin D, which helps the body absorb calcium from food, also is associated with hip fracture risk.

→ Cawthon PM, et al. *J Bone Miner Res* 2009;24(10):1728-35. PMID: 19419308. PMCID: PMC2743283.
Cauley JA, et al. *Ann Intern Med* 2008;149(4):242-50. PMID: 18711154. PMCID: PMC2743412.
Mackey DC, et al. *JAMA* 2007;298(20):2381-8. PMID: 18042915.
Sahni S, et al. *Osteoporos Int* 2009;20(11):1853-61. PMID: 19347239. PMCID: PMC2766028.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/11_28.asp
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/low_vitD_hip_fracture.asp
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIAMS**, NCRR, NHLBI, NIA)

The Hispanic Community Health Study: In October 2006, NIH began the largest long-term epidemiological study of health and disease ever conducted in people of Hispanic/Latino heritage living in the United States. The study includes 16,000 participants of diverse Hispanic/Latino background, including Mexican, Cuban, Puerto Rican, and Central/South American. It is designed to identify factors that render these groups either susceptible to or protected from heart disease, stroke, asthma, chronic obstructive pulmonary disease, sleep disorders, dental disease, hearing loss, diabetes, kidney and liver disease, cognitive impairment, and other chronic conditions. Recruitment started in March 2008 in four cities. Variables such as height, weight, and other body measurements; blood pressure; blood lipids and glucose levels; diet; physical activity; smoking; acculturation; socioeconomic status; psychosocial factors; occupational history and exposure; access to and use of health care services; and use of medications and dietary supplements currently are being assessed.

→ For more information, see http://www.cscc.unc.edu/hchs
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NHLBI**, NCMHD, NIDCD, NIDCR, NIDDK, NINDS, ODP/ODS)

The Multi-Ethnic Study of Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter epidemiological study of cardiovascular disease (CVD) in 6,914 men and women from 4 ethnic groups—white, African-American, Hispanic, and Chinese—who have been followed for almost 10 years to identify predictors of progression of subclinical CVD. The study originally was funded from 1999 to 2008 and subsequently renewed through 2015. It has measured and compared the predictive value of chest computed tomography, cardiac magnetic resonance imaging, carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for the development of CVD. MESA has major ongoing ancillary studies in the areas of air pollution (funded by the EPA), chronic lung disease, and genetics. MESA SHARe (SNP Health Association Resource) will combine genome-wide scans

with detailed phenotypic information and share these data with the scientific community for genome-wide association analyses.

→ For more information, see http://mesa-nhlbi.org
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*
→ (E) (**NHLBI**, NEI)

The Strong Heart Study: The Strong Heart Study was initiated in 1988 to estimate the morbidity and mortality from cardiovascular disease (CVD) in 3 geographically diverse groups of American Indians and to estimate the levels of CVD risk factors in 4,549 adult men and women aged 45-74 in 3 centers. It evolved into a study of large families after a successful pilot study in each center. The original cohort was examined three times and continues to be followed for morbidity and mortality. The family study currently is completing its second examination and has conducted a linkage study of multiple cardiovascular phenotypes.

→ For more information, see http://strongheart.ouhsc.edu
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NHLBI**)

Genetics of Coronary Artery Disease in Alaska Natives Study: This is a study of large families of Alaska natives (Eskimos) living in Nome and surrounding villages. Recruitment of 1,214 individuals in approximately 40 families has been accomplished. A genome-wide scan of almost 400 microsatellite markers and linkage analyses with cardiovascular disease risk factors and subclinical disease measures were completed recently to search for relevant genes. Phase II is nearing completion and will establish surveillance of the cohort, add four villages that were part of a previous study following a similar protocol, conduct a second examination on the cohort, and pursue significant linkage findings.

→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NHLBI**)

The Coronary Artery Risk Development in Young Adults (CARDIA) Study: CARDIA is studying the distribution and evolution of risk factors for cardiovascular disease (CVD) during young adulthood in 5,115 African-American and white men and women who were aged 18-30 years when the study began in 1985. The project has completed 7 examinations of these participants over 20 years. CARDIA has measured standard CVD risk factors at all examinations to permit analyses of secular trends and interrelationships among risk factors. Measures of subclinical CVD, such as coronary artery calcium, carotid intima-media wall thickness, arterial compliance, and left ventricular mass and function also have been assessed. DNA will be analyzed to elucidate how genetic variability and gene-environment interactions may explain differences in the severity and progression of CVD. Major objectives for the upcoming eighth examination include identifying early adulthood antecedents and consequences of obesity, understanding the determinants and trajectories of CVD development in women during the menopausal transition, and further assessing the basis for racial differences in the development and progression of CVD.

→ For more information, see http://www.cardia.dopm.uab.edu
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NHLBI**)

Genetic Epidemiology of COPD (COPDGene): This investigator-initiated research program is performing genetic testing in more than 10,000 current or former smokers to identify genes that are associated with the presence of COPD (chronic obstructive pulmonary disease). In this large and diverse cohort, half of the subjects will be women and one-third

will be African American. Although COPD is the fourth most common cause of death in the United States, understanding why some smokers develop serious lung disease and others do not is lacking. Genetics studies may reveal factors that determine this differential susceptibility to disease. The COPDGene study will help to identify individuals at greatest risk, point to particular molecular pathways that may be involved in pathogenesis, and suggest possible targets for prevention and drug therapy. The phenotypic and genetic data generated by the program will be made available through an NIH data repository to allow additional research analyses by other investigators. COPDGene has thus far enrolled more than 4,000 subjects at 17 sites across the United States.

→ This example also appears in Chapter 3: *Genomics*
→ (E) (**NHLBI**)

The Collaborative Study on the Genetics of Alcoholism (COGA): In its 20th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) that are densely affected by alcoholism, enabling researchers to take a multigenerational perspective. A recent COGA study focusing on adolescents follows individuals longitudinally as they transition through the age of risk. Investigators have identified several genes, including *GABRA2, ADH4, ADH5, CHRM2, GRM8, GABRR1*, and *GABRR2* (*Rho 1* and *2*) that influence the risk for alcoholism and related behaviors, such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected, and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes that influence vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

→ Xuei X, et al. *Am J Med Genet B Neuropsychiatr Genet* 2009;150B(3):359-68. PMID: 19536785. PMCID: 2829340.
→ For more information, see http://zork.wustl.edu/niaaa
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Genomics*
→ (E) (**NIAAA**) (GPRA)

Unraveling the Complexity of the Genetics of Glaucoma: Glaucoma is a group of eye disorders that share a distinct type of optic nerve damage, which can lead to blindness. It is the leading cause of blindness in African Americans. More than 2 million Americans have been diagnosed with glaucoma, and the prevalence of the disease will rise to a projected 3 million by 2020. Glaucoma research aims to understand the complex genetic factors that lead to common forms of the disease and to develop treatments that protect ganglion cells of the retina from the damage that leads to vision loss. Under GPRA, NIH set a goal by 2012 to identify the genes that control the risk of glaucoma. To achieve this goal, NIH launched a large genome-wide association study to identify glaucoma risk genes. NEIGHBOR (NEI Glaucoma Human Genetics CollaBORation) is a unique collaborative effort involving 22 investigators at 12 institutions throughout the United States. Approximately 2,000 cases and 2,000 age, sex, and ethnically matched controls will have their complete genome sequenced (genotyped) for a genome-wide association study to identify genetic variants associated with the disease. Genetic data and associated disease characteristics collected from NEIGHBOR will be made available to the research community through the NIH database of Genotypes and Phenotypes (dbGaP).

→ Friedman DS, et al. *Arch Ophthalmol* 2004;122(4):532-8. PMID: 15078671.
→ For more information, see http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/about.html
→ This example also appears in Chapter 3: *Genomics*
→ (E) (**NEI, NLM**) (GPRA)

Studies of Diabetes in Youth: NIH and CDC support the SEARCH for Diabetes in Youth study, which is providing key data on childhood diabetes incidence and prevalence. Recent data from SEARCH revealed unexpectedly high rates of diabetes in youth across most ethnic and racial groups in the United States. SEARCH also estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. To address the emerging problem of type 2 diabetes in youth, NIH supports the HEALTHY multicenter study to prevent risk factors for type 2 diabetes in middle-school children. A pilot study for HEALTHY found that an alarmingly high 15 percent of students in middle schools enrolling mainly minority youth had 3 major risk factors for type 2 diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease risk for obesity and diabetes. Thus, NIH launched the HEALTHY study in 2006. Half of the 42 participating middle schools receive the intervention, which includes changes to school food service and physical education classes, behavior change, and communications campaigns. More than 70 percent of the enrolled students are from minority populations. For children who already have been diagnosed with type 2 diabetes, NIH supports the Treatment Options for Type 2 Diabetes in Youth (TODAY) study, which is comparing three different treatment strategies for children with the disease.

→ Mayer-Davis EJ, et al. *Diabetes Care* 2009;32 Suppl 2:S99-101. PMID: 19246580. PMCID: PMC2647691.
→ For more information, see http://www.searchfordiabetes.org/
→ For more information, see http://www.todaystudy.org/index.cgi
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**, CDC)

Childhood and Maternal Obesity: As the maternal and childhood obesity epidemic widens, researchers are trying to understand the interaction among the many complex biological and behavioral factors that contribute to this rise, identify the long-term impact on mother and child, and develop effective interventions to reverse these trends. NIH obesity research, which includes a range of racial and ethnic groups, is examining such topics as:

- Basic research on the physiology, psychology, and genetics of obesity in children.
- Developing community-based partnerships to prevent and control childhood obesity.
- Applying computational and statistical methodologies to design and analyze multilevel studies on childhood obesity. Multilevel studies include those that consider the range of biological, family, community, sociocultural, environmental, policy, and macro-level economic factors that influence diet and physical activity in children.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-09-140.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-023.html
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E/I) (**NICHD**, NCI, NHLBI, OBSSR)

Genetics of Diabetes: Diabetes is a common, potentially deadly and debilitating chronic disease that poses an enormous health care burden. Both of the most common forms of diabetes, type 1 and type 2, are caused by an intersection of genetic and environmental risk factors. Although genetic effects on developing diabetes are profound, they are not simple, as there are many genes that influence the likelihood of developing type 1 or type 2 diabetes. Further, ethnicity impacts both genetic and environmental risk factors. To learn more about diabetes genetics, particularly through new genomic technologies, NIH supports the Type 1 Diabetes Genetics Consortium to study type 1 diabetes, and several major grants to study the genetics of type 2 diabetes. These programs now have identified at least 40 genetic regions linked to type 1 diabetes and at least 38 type 2 diabetes genes. Other studies are refining our understanding of how these genes affect diabetes risk. Many of these projects are geared to collect data from multiple ethnic groups, but a recent initiative sought to advance knowledge of diabetes risk genes in specific racial and ethnic groups disproportionately affected by type 2 diabetes, to understand how different genes affect different populations.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-004.html
→ For more information, see http://www.t1dgc.org
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Genomics*
→ (E) (**NIDDK**, NHGRI, NIAID, NICHD)

The Sister Study: Environmental Risk Factors for Breast Cancer: The NIH Sister Study prospectively examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The frequency of relevant genes and shared risk factors is greater among sisters, increasing the ability of the study to detect risks. Researchers will collect data on potential risk factors and current health status, and will collect and bank blood, urine, and environmental samples for future use in studies of women who develop breast cancer or other diseases compared with those who do not. Analysis of new cases will assess the separate and combined effects of environmental exposures and genetic variations that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors like smoking, occupational exposures, alcohol, diet and obesity, and include analysis of phthalates, phytoestrogens, metals, insulin, growth factors, vitamins and nutrients, and genes in blood and urine. The study also allows investigators to examine a wide range of health outcomes of relevance to women, and to create a framework from which to test new hypotheses as they emerge. In addition to its focus on genetic and environmental causes of breast cancer, the prospective Sister Study tracks changes in health status over time. Among the chronic diseases currently studied are uterine fibroids and endometriosis, rheumatoid arthritis and other autoimmune diseases, thyroid disease, asthma, and cardiovascular diseases. As the cohort ages, the Sister Study will address aging-related health outcomes including osteoporosis, Parkinson's disease, and age-related cognitive decline.

→ For more information, see http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E/I) (**NIEHS**, NCMHD)

The Osteoarthritis Initiative: A limited number of therapies exist for osteoarthritis (OA) treatment. Most only relieve pain and reduce disability; none slows or halts disease progression. One barrier to the development of drugs that block the underlying causes of OA symptoms is the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. To overcome this problem, NIH—with input from FDA—partnered with private sponsors to create the Osteoarthritis Initiative (OAI). When complete, the OAI will provide an unparalleled state-of-the-art database showing both the natural progression of the disease and information on risk factors, joint changes, and outcome measures. All data will be freely available to researchers worldwide, who can develop hypotheses about possible OA biomarkers of disease onset and progression, test their theories, describe the natural history of OA, and investigate factors that influence disease development and severity. Scientists also can use the OAI to identify potential disease targets and to develop tools for measuring clinically meaningful improvements. The OAI originally was to receive funding through FY 2009, during which time investigators would collect survey, clinical, and image data and biological samples from approximately 4,800 people at baseline, 12-, 24-, 36-, and 48-month time points. NIH extended the study to include 72- and 96-month data. By the end of FY 2009, more than 1,350 researchers from 54 countries had registered to access OAI data. A total of 4,100 clinical datasets have been downloaded. In FYs 2008 and 2009, more than 18 articles using OAI data were accepted for publication in peer-reviewed journals.

→ For more information, see http://www.niams.nih.gov/Funding/Funded_Research/Osteoarthritis_Initiative
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAMS**, NCCAM, NCMHD, NIA, NIBIB, NIDCR, ORWH) (GPRA)

Genetics of Chronic Kidney Disease: Researchers recently have made progress in uncovering the role of genetics in chronic kidney disease (CKD) arising from various causes. Scientists recently have identified a genetic region that is strongly associated with CKD in African Americans that arises as a consequence of conditions other than diabetes, such as high blood pressure and HIV-associated kidney disease. Several variants associated with the *MYH9* gene were identified as major contributors to excess risk of this kind of CKD among African Americans. This finding suggests that CKD may proceed along different paths depending on whether diabetes or another condition is the underlying disorder. The Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to study progression of an inherited form of kidney disease, polycystic kidney disease (PKD). Phase I of the study demonstrated that magnetic resonance imaging accurately could track structural changes in the kidneys; Phase II showed that patients with mutations in the *PKD1* gene have more cysts and larger kidneys than patients with *PKD2* mutations. A planned third phase of CRISP will provide critical information about the validity of changes in kidney volume as a surrogate marker for loss of kidney function. NIH also has launched a study to identify and validate biomarkers and risk assessment tools for kidney function, injury, and disease progression in patients with CKD, to predict risk, aid early diagnosis, and assess disease progression.

→ Kopp JB, et al. *Nat Genet* 2008;40(10):1175-84. PMID: 18794856.
Kao WHL, et al. *Nat Genet* 2008;40(10):1185-92. PMID: 18794854. PMCID: PMC2614692.
Grantham JJ, et al. *New Engl J Med* 2006;354(20):2122-30. PMID: 16707749.
Rule AD, et al. *J Am Soc Nephrol* 2006;17(3):854-62. PMID: 16452494.
→ For more information, see http://www.nih.gov/news/health/sep2008/niddk-14.htm
→ For more information, see http://www.nih.gov/news/pr/may2006/niddk-17.htm
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Genomics*
→ (E/I) (**NIDDK**, AHRQ, NCI, NCRR, NHLBI)

Diabetes Prevention Program Outcomes Study (DPPOS) and Translational Research: The landmark NIH Diabetes Prevention Program (DPP) clinical trial showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk. This finding was true across all participating ethnic groups and for both men and women. The DPPOS is a long-term follow-up study of the DPP participants that is determining the durability of the interventions in preventing or delaying type 2 diabetes, and how the interventions affect the development of cardiovascular disease and other complications of diabetes. The DPP group was highly diverse (45 percent from minority ethnic and racial groups), and DPPOS will compare outcomes for women and men, and by age and ethnicity. Renewed in FY 2009 for a second 5-year phase, the DPPOS will enable researchers to better determine the lasting benefits of the interventions to diabetes prevention and/or the delay of onset. In addition, NIH is pursuing translational research efforts to develop more cost-effective methods of achieving the lifestyle change that delayed or prevented diabetes in the DPP, and better methods to identify those with prediabetes. For example, one translational effort is using the YMCA to deliver a DPP lifestyle intervention; data from a recent pilot study suggest that using the YMCA may be a low-cost way to deliver a lifestyle intervention to large numbers of people in the United States. Many of these translational research studies focus on minority populations disproportionately burdened by type 2 diabetes and by obesity, a significant risk factor for type 2 diabetes.

→ For more information, see http://www.bsc.gwu.edu/dpp/protocol.htmlvdoc
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-09-176.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-06-532.html
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**, CDC, IHS, NEI, NHLBI, NIA, NICHD, NINR, OBSSR, ORWH)

Prevention of Diabetes in Women with a History of Gestational Diabetes: A past history of gestational diabetes mellitus (GDM) confers a very high risk of postpartum development of diabetes, particularly type 2 diabetes in women. This ancillary study of the Diabetes Prevention Program was a multicenter, randomized, controlled clinical trial of: 1) standard lifestyle/placebo, 2) standard lifestyle and metformin therapy, or 3) an intensive lifestyle intervention, and was conducted at 27 academic centers and Indian Health Services sites with a total of 2,190 women involved. The investigators found that in women with the same glucose levels at the beginning of the study, women with a history of GDM had a crude incidence rate of diabetes 71 percent higher than that of women without such a history. They also found that among women reporting a history of GDM, the reduction in the incidence of diabetes was approximately 50 percent for both the intensive lifestyle modification and metformin group compared with the placebo group. This ancillary study demonstrated that both intensive lifestyle and metformin are highly effective in delaying or preventing diabetes in women with a history of GDM.

→ For more information, see http://jcem.endojournals.org/cgi/content/full/93/12/4774
→ For more information, see http://ndep.nih.gov/
→ For more information, see http://diabetes.niddk.nih.gov/
→ (E) (**ORWH**, NIDDK)

NIH Committee on the Science of Behavior Change (SOBC): A key national goal, at the scientific and policy level, is to eliminate preventable diseases and their associated disabilities and premature deaths. To achieve this goal, the science of behavior change increasingly is being recognized as a critical area for research. While NIH historically has invested in biobehavioral research, SOBC is a crucial step to coordinate, leverage, and advance these efforts. The SOBC initiative examines topics that span the continuum of behavior change and across disciplines. The SOBC goals include the identification of new and productive paradigms for SOBC research—paradigms that will facilitate the synthesis, integration, and application of SOBC research; that will help to bridge the distances that often separate investigators and disciplines; and that will inform and identify future research directions and initiatives. On June 15-16, 2009, NIH brought together experts in the fields of basic and applied behavioral sciences, genetics, economics, and methodology with the goal of advancing an NIH-wide agenda on the science of behavior change. The main topics of discussion were the acquisition and prevention of behavior, changing existing behavior, and maintenance of behavior. The SOBC working group will use ideas generated from the meeting to develop new interdisciplinary initiatives in behavior change research.

→ For more information, see http://nihroadmap.nih.gov/documents/SOBC_Meeting_Summary_2009.pdf
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NINR, NIA**, DPCPSI, FIC, NCCAM, NCI, NHGRI, NHLBI, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIGMS, NIMH, NINDS, OBSSR)

Strategies to Manage and Prevent Food Allergies: Food allergy occurs in approximately 4.7 percent of children under 5 years of age and in 3.7 percent of children 5 to 17 years of age. Allergies to peanuts and tree nuts, the allergens most relevant to severe food allergy and anaphylaxis, occur in approximately 1 percent of children and adults. Severe whole-body allergic reactions, also known as anaphylaxis, are a frequent cause of emergency room visits, many of which are attributed to food allergy. Every year in the United States, it is estimated that there are approximately 15,000-30,000 episodes of food-induced anaphylaxis. NIH seeks to understand better both the immune system response to food allergies and how certain foods trigger an allergic reaction. Researchers in the United States and abroad are conducting clinical trials to improve management of allergy to cow's milk, egg, and peanut, and innovative clinical trials are assessing strategies to prevent development of peanut allergies. One important trial will determine whether early and regular consumption of a peanut snack by infants and very young children at risk of developing peanut allergy will promote tolerance and prevent the development of this allergy. In FY 2008, NIH sought to bring new investigators into the field through the Exploratory Investigations in Food Allergy initiative, which supports innovative pilot studies and developmental research on the mechanisms of food allergy. The program will be recompeted in FY 2010. During this

period, NIH continued funding for the Consortium of Food Allergy Research, which supports basic, preclinical, and clinical research to assess the pathophysiology and natural history of food allergy-associated anaphylaxis and to develop interventions to prevent and treat food allergy.

→ For more information, see http://www3.niaid.nih.gov/topics/foodAllergy/default.htm
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAID**)

Preventing Drug Abuse in Children and Adolescents: Intervening early to reduce risk factors for drug abuse and related problem behaviors can have tremendous impact and improve the trajectory of a young life. NIH is using a multipronged approach to achieve more effective substance abuse prevention by: (1) developing novel strategies, (2) exploring long-term and crossover effects of proven programs, and (3) improving adoption and implementation of evidence-based approaches. Innovative ideas being explored include physical activity to counter drug use, interactive Web-based technologies to engage young people, and brain imaging results to better target media messages. NIH also is building on proven methods such as universal prevention programs, which can reduce an array of risk behaviors, including substance abuse. These programs typically target behaviors appropriate to a child's developmental stage and have been shown to achieve long-term effects. For example, fifth graders who participated in the school-based prevention program "Positive Action" as first graders were about half as likely to engage in substance abuse, violent behavior, or sexual activity as those who did not. Similarly, exposure to the "Good Behavior Game," designed to reduce aggressive, disruptive behavior in first and second grade classrooms, led to fewer drug and alcohol disorders, lower rates of regular smoking, less antisocial personality disorder, and reduced delinquency and violent crime in young adults. However, the development of evidence-based prevention programs is meaningless unless they are adopted by communities. Therefore, NIH also is striving to increase implementation of successful prevention approaches in U.S. schools and communities.

→ Beets MW, et al. *Am J Public Health* 2009;99(8):1-8. PMID: 19542037.
Kellam SG, et al. *Drug Alcohol Depend* 2008;95 Suppl 1:S5-S28. PMID: 18343607. PMCID: PMC2512256.
Spoth R, et al. *Am J Prev Med* 2007;32 (5):395-402. PMID: 17478265.
→ For more information, see http://www.nida.nih.gov/scienceofaddiction/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**)

The Rapid Response Program: In April 2002, NIH issued a major report on college drinking: *A Call to Action: Changing the Culture of Drinking at U.S. Colleges*. This report was developed by the NIH-supported Task Force on College Drinking, a group consisting of college presidents, researchers, students, and NIH staff. The report describes the magnitude of mortality and morbidity resulting from dangerous drinking behavior by college students and the consequences for both drinkers and nondrinkers. In addition, interventions found through rigorous research to reduce college drinking were reviewed. A copy of the report was mailed to every U.S. college president in 2002, as was the NIH report *What Colleges Need to Know Now: An Update on College Drinking Research in 2007*. In 2002-2003, NIH issued two RFAs: "Research Partnership Awards for Rapid Response to College Drinking Problems" and "Rapid Response to College Drinking Problems." From the applications in response to these RFAs, 5 investigators were matched with 15 colleges and universities to test a variety of individual, counseling, academic, policy, and community/campus partnership interventions to reduce college drinking, including residential learning communities, peer-facilitated alcohol interventions, peer-led motivational enhancement with freshmen women, freshmen parent-student initiatives, fraternity and sorority interventions, alcohol screening in a college health clinic, social norms programs, and a university assistance programs. Findings from these and some of NIH's 32 other grants examining college drinking prevention are available in a special June 2009 issue of the *Journal of Studies on Alcohol and Drugs*, which includes 15 articles related to this topic.

→ Hingson RW, et al. *J Stud Alcohol Drugs Suppl* 2009;(16):12-20. PMID: 19538908. PMCID: PMC2701090.
Faden VB, et al. *J Stud Alcohol Drugs Suppl* 2009;(16):28-33. PMID: 19538910. PMCID: PMC2701094.
Schaus JF, et al. *J Stud Alcohol Drugs Suppl* 2009;(16):131-141. PMID: 19538921. PMCID: PMC2701092.
Saltz RF, et al. *J Stud Alcohol Drugs Suppl* 2009;(16):21-7. PMID: 19538909. PMCID: PMC2701100.
Amaro H, et al. *J Stud Alcohol Drugs Suppl* 2009;(16):45-56. PMID: 19538912. PMCID: PMC2701089.
→ For more information, see http://www.jsad.com/jsad/articles/Sup/16/260.html
→ (E) (**NIAAA**)

Underage Drinking Research Initiative: In 2004, NIH launched its Underage Drinking Research Initiative with the goal of obtaining a more complete and integrated scientific understanding of the environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence—all framed within the context of overall human development. Activities and accomplishments in 2008 and 2009 include: (1) working with the Office of the Surgeon General to disseminate *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking*, including state roll-outs in Oklahoma, Ohio, Nebraska, Wyoming, Montana, Maryland, and Rhode Island (in addition to the six held in 2007); (2) continuing to convene scientific meetings of experts to advance underage drinking research. A series of meetings focusing on the development of guidelines and recommendations for screening children and adolescents for risk for drinking, alcohol abuse, and alcohol use disorders continued in 2008-2009; (3) issuing RFAs and program announcements (PAs), including "Limited Competition: Underage Drinking: Building Health Care System Responses (Phase II)" (RFA-AA-09-001) and "Alcohol, Decision-Making, and Adolescent Brain Development" (PA- 09-097 (R01) and PA-09-096 (R21)); (4) published "A Developmental Framework for Underage Alcohol Use"; and (5) published a *Pediatrics* supplement of seven developmentally focused papers covering a broad range of underage drinking topics.

→ A Developmental Perspective on Underage Alcohol Use. *Alcohol, Research and Health* 2009;32(1). Available at: http://pubs.niaaa.nih.gov/publications/arh321/toc32-1.htm.
Masten AS, et al. *Pediatrics* 2008;121 Suppl 4:S235-51. PMID: 18381492. Available at: http://pediatrics.aappublications.org/cgi/reprint/121/Supplement_4/S235.
→ For more information, see http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E, O) (**NIAAA**)

Addressing Drug Abuse and Comorbidities in Returning Vets and Their Families: Sustained U.S. combat operations in Afghanistan and Iraq have resulted in military personnel experiencing increased numbers and lengths of deployments and greater exposure to traumatic stressors. Stress can be a major contributor to both the onset and exacerbation of substance abuse and other mental health problems, and can lead to relapse in former substance abusers. To understand better the intervention needs of this group, NIH in 2009 sponsored a 2-day meeting to formulate a research agenda for conducting addiction prevention and treatment research with military and veteran populations and their families. Collaborators included the U.S. Army Medical Research and Materiel Command, the Department of Defense Health Affairs, the Army Center for Substance Abuse Programs, the Department of Veterans Affairs, and several NIH ICs. Subsequently, a call for studies on trauma, stress, and substance use and abuse among U.S. military personnel, veterans, and their families was issued. It focuses on epidemiology/etiology, screening and identification, and prevention and treatment of substance use and abuse—including alcohol, tobacco, and other drugs—and associated problems (e.g., PTSD, traumatic brain injury, sleep disturbances, and relationship violence) among U.S. military personnel, veterans, and their families. Further, NIH's National Drug Abuse Treatment Clinical Trials Network (CTN) is developing a protocol concept for the treatment of PTSD and drug abuse/dependence in veteran populations. It is expected that this study will be conducted in clinics participating in the CTN, which include some Veterans Administration hospitals and research facilities.

→ For more information, see http://www.drugabuse.gov/pdf/tib/veterans.pdf

→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIDA**, NCI, NIAAA, NIMH)

Exercise Guide for Older Americans: In January 2009, NIH offered an update of its popular exercise guide, newly titled *Exercise and Physical Activity: Your Everyday Guide from the National Institute on Aging*. The guide is the result of a 2-year process overseen by the Task Force on Exercise and Physical Activity, which included top scientists conducting research on exercise and physical activity in older adults, as well as representatives from key organizations involved in promoting exercise and physical activity to the public, including CDC, the American College of Sports Medicine, and the International Council on Active Aging. Based on an intensive review by these experts of the evidence on physical activity, the updated publication reviews in lively, easy-to-understand language the benefits of physical activity for older people, discusses the importance of regular effort and goal setting, provides specific activities and exercises appropriate for varying strength and skill levels, and includes worksheets to help the reader track his or her progress. The new guide is proving popular already with the public; between 2000 and 2008, NIH distributed 1.2 million copies while in 2009, NIH has distributed more than 300,000 copies of the guide. NIH is undertaking an outreach effort on exercise, with the guide as a foundation, to encourage older people to become more physically active.

→ For more information, see http://www.nia.nih.gov/Exercise
→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (O) (**NIA**)

A Multidisciplinary Approach to Tobacco Addiction: Tobacco addiction is the number one preventable public health threat, with enormous associated morbidity, mortality, and economic costs. Cigarette smoking—powerfully addictive mainly because of the key ingredient nicotine—is the greatest preventable cause of cancer, accounting for at least 30 percent of all cancer deaths, 87 percent of lung cancer deaths, and nearly 80 percent of deaths from chronic obstructive pulmonary disease, according to CDC. CDC also reports that these leading causes of death could become relatively uncommon in future generations were the prevalence of smoking substantially reduced. In that vein, NIH-supported research has led to major advances in critical areas that together could greatly enhance our ability to either prevent or mitigate the impact of tobacco addiction. Convergent genomic studies recently have uncovered several genes previously not associated with nicotine reward or addiction that convey increased risk for addiction. This finding identifies markers of vulnerability, as well as new targets for medications development, with the potential to personalize, and thereby improve, treatment based on patients' genetic profiles. Clinical trials are exploring new medications and behavioral therapies for tobacco addiction. A promising approach, which already completed Phase II clinical testing, is that of immunotherapy. A nicotine vaccine (NicVAX), which binds nicotine in the blood, preventing it from ever reaching the brain, showed strong positive results in promoting abstinence among study participants who achieved sufficient antibody levels. Further studies are helping to define optimal protocols for vaccination to improve results in all smokers. This may be a particularly useful tool for tobacco cessation programs in the not-too-distant future.

→ Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and productivity losses United States, 1997-2001. *Morb Mortal Wkly Rep* 2005;54:625-8.
Centers for Disease Control and Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses United States, 2000-2004. *Morb Mortal Wkly Rep* 2008;57(45):1226-28.
Institute of Medicine. *Ending the Tobacco Problem: A Blueprint for the Nation.* Washington, DC: National Academies Press; 2007.
→ For more information, see http://www.drugabuse.gov/ResearchReports/Nicotine/Nicotine.html
→ For more information, see http://cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDA**, NCI) (GPRA)

SNP-Health Association Resource (SHARe): SHARe conducts genome-wide association studies in several large NIH cohort studies to identify genes underlying cardiovascular and lung diseases and other disorders such as obesity and diabetes. The resulting genotype data along with the cohort phenotype data are made available to researchers around the world through the NIH dbGAP database. Framingham SHARe, with 9,000 participants, was the first cohort released in this initiative due to its uniqueness in including 3 generations of participants with comparable data obtained from each generation at the same age. As of October 31, 2009, 95 projects to use these data had been approved. A modified version of the dataset was distributed to 72 approved research projects as the focus of a Southwest Foundation Genetic Analysis Workshop. The second cohort released was the SHARe Asthma Resource Project, which includes genotype data from more than 2,500 adults and children who have participated in NIH clinical research trials on asthma. As of October 31, 2009, 11 projects to use these data had been approved. Data from more than 12,000 African-American and Hispanic women from the Women's Health Initiative and approximately 8,300 participants from the Multi-Ethnic Study of Atherosclerosis were released in January 2010.

→ For more information, see http://www.nih.gov/news/pr/oct2007/nhlbi-01.htm
→ For more information, see http://nih.gov/news/health/dec2008/nhlbi-15.htm
→ For more information, see http://view.ncbi.nlm.nih.gov/dbgap/
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*
→ (E) (**NHLBI**, NLM)

Genome-Wide Association Studies: With unprecedented speed, researchers have used an approach called genome-wide association studies (GWAS) to explore genetic variants and their complex relationships to human health and disease. GWAS research has linked a stunning number of genetic variants to common conditions—more than 130 in 2008 alone. For example, the obesity epidemic and its related health conditions pose a great challenge for the Nation. In 2008, the Genetic Investigation of Anthropometric Traits consortium identified six genes associated with body mass index, a key indicator for obesity. Also in 2008, three GWAS of lung cancer implicated several genes already known to be linked to nicotine addiction. In a feat that would not have been possible without the power of whole genome analysis, the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium in 2009 gathered data from participants in long-running studies to reveal genetic variants associated with an increased risk of stroke. Identification of genetic variants associated with common diseases opens new windows into the biology of health and disease. This work also raises the possibility of someday using genetic testing, in combination with family history, to identify at-risk, pre-symptomatic individuals who might benefit from personalized screening and preventive therapies.

→ For more information, see http://www.genome.gov/27528559
→ For more information, see http://www.genome.gov/27529231
→ For more information, see http://www.genome.gov/27531390
→ This example also appears in Chapter 2: *Cancer*, Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E, I) (**NHGRI, NIDDK, NCI, NIA, NHLBI, NIMH**, NINDS)

Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE): A large body of research in animals indicates that substantially reducing caloric intake while maintaining optimal nutrition can significantly lengthen life span. The CALERIE study will help to determine if these effects extend to humans. This long-term study began in January 2007 and is ongoing. Recently, CALERIE researchers used state-of-the-art techniques to measure metabolic changes that occur in response to caloric restriction with or without exercise. They found that energy metabolism slows in response to caloric restriction, but the addition of exercise to a caloric restriction regimen may forestall such a “metabolic adaptation,” potentially explaining why a combination of dietary restriction and exercise, as opposed to dietary restriction alone, may be the best intervention to sustain weight loss. Overall, these findings provide important information about the mechanisms of weight loss and indicate that exercise may be an important component of a weight loss regimen.

→ For more information, see http://calerie.dcri.duke.edu
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIA**)

NIEHS Clinical Research Unit: NIEHS focuses its research mission on environmental effects on human health, an area where human research data often are lacking. To improve the translation of basic research to human health, the NIEHS is expanding its Clinical Research Program (CRP). NIEHS has opened a new Clinical Research Unit (CRU) on the Research Triangle Park, NC, campus. The mission of the CRP is to translate basic laboratory findings to humans; study interactions between genetic susceptibility and environmental factors in the pathogenesis of complex human traits and diseases; and identify populations at risk and develop novel preventative and therapeutic strategies to combat human diseases. The CRU will provide support for the development of clinical research protocols; provide patient screening, recruitment and enrollment functions for NIEHS clinical studies; provide basic sample processing support (e.g., clinical labs and cell isolation); and provide support for specialized clinical procedures and services with the ultimate vision of fostering substantial onsite clinical research activity. Examples of the kinds of studies that will be supported by the CRU include the following: collection of tissue and body fluid samples for *ex vivo* human studies; investigation of host response to environmental exposures; Phase I-II-III clinical trials; environmental intervention studies; and phenotyping of selected individuals from NIEHS research populations such as the Environmental Polymorphism Registry. The CRU will be an integral part of the NIEHS intramural research portfolio and will provide support to a substantial number of NIEHS scientists.

→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (I) (**NIEHS**)

Comorbidity of Depression with Other Chronic Diseases: Major depressive disorder is the leading cause of disability in the United States and affects approximately 14 million American adults annually. Depression frequently occurs among individuals with other medical conditions, such as advanced heart disease, Parkinson's disease, and diabetes. Despite the increased risk of depression in the presence of other medical illnesses, comorbid depression is not typically recognized or adequately treated, particularly over the course of chronic illnesses. NIH is undertaking multiple strategies to guide efforts at reducing the years lost to disability as a result of comorbid depression. A GPRA goal was developed to synchronize research efforts focused on early detection, prevention, and treatment of depressive disorders, and their relationship to other chronic diseases. The quality of care available to persons with treatment-resistant depression, as well as treatment for persons with depression that is comorbid with other medical illnesses, will improve as (1) knowledge of the causes and processes of depression expands, including the genetic, environmental, behavioral, and cultural risk and protective factors; (2) psychosocial and pharmacological treatments become more refined and targeted; and (3) strategies are developed for protecting individuals from relapse and recurrence of depression.

→ (E/I) (**NIMH**) (GPRA)

Comorbidity: Addiction and Other Mental Disorders: Drug addiction frequently is accompanied by other psychiatric diseases, which can complicate its diagnosis and treatment. Thus, NIH supports research on the multiple facets of psychiatric comorbidity across multiple health sectors. This approach explores whether drug use leads to mental illness or the reverse, what causes their frequent co-occurrence (e.g., shared genetic and environmental vulnerabilities or similarities in brain circuits and chemical messengers), and how to treat both comprehensively. Specific activities include epidemiological research on mental health/drug abuse comorbidity, such as secondary analyses of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study and the National Comorbidity Survey to better understand the prevalence and variety of comorbidities, and clinical trials to help assess the actions of combined or dually effective behavioral and medication treatments (e.g., in adolescent and adult patients with attention

deficit/hyperactivity disorder [ADHD] and substance abuse problems). It also includes a push for research to investigate drug abuse and mental health screening for all those entering the criminal justice system, a notable gap, particularly for adolescents. Another identified gap calls for research using preclinical models of comorbidity to explore the neurological bases of comorbid drug abuse and other mental illness (e.g., overlapping circuitry). Joint requests for applications issued by multiple ICs have elicited studies examining everything from the role of depression and anxiety in the tobacco epidemic to the neural bases of ADHD in fetal drug or alcohol exposure to improving care for co-occurring disorders in rural areas via new technologies. (Note: NESARC and the National Comorbidity Survey are nationally representative surveys in the United States that assess the prevalences and correlates of DSM-III-R disorders, including substance use and mental health disorders.)

→ For more information, see http://www.drugabuse.gov/CTN/protocol/0028.html
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0029.html
→ For more information, see http://www.nida.nih.gov/ResearchReports/comorbidity
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**, NIAAA, NIMH)

Advances in Understanding the Genomic Risk for Schizophrenia: Three genome-wide studies have pinpointed a vast array of genetic variation that cumulatively poses the greatest risk for schizophrenia yet reported. All three studies implicate an area of chromosome 6 (6p22.1), which is known to harbor genes involved in immunity and genes that control how and when genes turn on and off. Among sites showing the strongest associations with schizophrenia was a suspect area on chromosome 22 and more than 450 variations in the suspect area on chromosome 6. Individually, these variants' effects statistically were insignificant, but cumulatively they were very powerful. Additionally, one of the studies traced schizophrenia and bipolar disorder, in part, to the same chromosomal neighborhoods. These findings suggest that if some of the same genetic risks underlie schizophrenia and bipolar disorder, then these disorders may originate from a common vulnerability in brain development.

→ Shi J, et al. *Nature* 2009;460(7256):753-7. PMID: 19571809. PMCID: PMC2775422.
Stefansson H, et al. *Nature* 2009;460(7256):744-7. PMID: 19571808.
International Schizophrenia Consortium, et al. *Nature* 2009;460(7256):748-52. PMID: 19571811.
→ This example also appears in Chapter 3: *Genomics*
→ (E) (**NIMH**)

Vitamin D Initiative: Vitamin D is an essential nutrient for maintaining health. In addition to enhancing calcium metabolism, accumulating evidence indicates that vitamin D may play other roles in human health, including supporting immune function; reducing inflammation; and supporting cell proliferation, differentiation, and programmed cell death. The importance of vitamin D to health has stimulated new research, resulting in growing concerns about the sufficiency of vitamin D levels in the U.S. population. To address these issues, NIH has established the Vitamin D Federal Working Group, which is translating the research needs in this area into actions by appropriate Federal research groups. The National Institute of Standards and Technology developed standard reference materials for vitamin D to facilitate analyses of vitamin D in foods and human fluids. The data on vitamin D collected through the National Health and Nutrition Examination Survey are being analyzed for trends in the nutritional status of the public. The NIH ICs are collaborating by providing funding opportunities to support research that will close the gaps in knowledge. NIH also expects that these vitamin D-related activities will inform the reappraisal by the Food and Nutrition Board of the Institute of Medicine of the dietary recommendations for vitamin D and calcium.

→ (E) (**ODP/ODS**)

Treating Chronic Disease and Comorbidities

Patient-Reported Outcomes Measurement Information System (PROMIS): The PROMIS initiative is developing new ways to measure patient-reported outcomes (PROs) for clinical research, such as pain, fatigue, physical functioning, emotional distress, and social role participation, which have a major impact on quality of life across a wide variety of chronic diseases. The first phase of PROMIS successfully has addressed its initial broad objectives of developing and testing a large item (survey question) bank for measuring PROs, along with translation of certain items into Spanish; creating a computer adaptive testing (CAT) system that allows for efficient, scientifically robust assessment of PROs in patients with a spectrum of chronic diseases; and producing a publicly available, Web-based system that continues to be updated and modified, to allow clinical researchers access to PROMIS resources, such as a common repository of validated items, a CAT system, and hard copy surveys. Preliminary results demonstrate that a short, 10-item PROMIS survey, administered by CAT, outperforms the most commonly used, paper-based, self-reporting assessment tool for arthritis disability (the Health Assessment Questionnaire). These results are indicative of the anticipated advantages of the PROMIS tool: better answers with fewer patients. The success of the project has garnered 4 more years of NIH funding for PROMIS. Prioritized tasks for PROMIS include validating and evaluating usability in future NIH-supported clinical trials, including Spanish translations; developing additional modes of administration; facilitating adoption of PROMIS by the clinical research community; and building partnerships to secure long-term sustainability for the PROMIS tools.

→ For more information, see http://nihroadmap.nih.gov/clinicalresearch/overview-dynamicoutcomes.asp
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIAMS**, Common Fund - all ICs participate)

Programs to Accelerate Medication Development for Alcoholism Treatment: Alcohol dependence is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ among individuals. Therefore, a diverse repertoire of medications is needed to provide effective therapy to a broad spectrum of alcohol-dependent individuals. Although promising compounds have been identified, developing medications is a long and costly process with a low probability of success for any single agent. NIH has initiated collaborations with the pharmaceutical industry to ensure its interest in taking promising compounds through the final phase of clinical trials and subsequent FDA consideration. As part of this approach, two new programs have been initiated:

- Laboratories have been established to screen promising compounds with animal models, enabling faster determination of those that merit advancement to large, multisite studies. Animal studies already have produced several targets for human studies that now are underway. The animal models are being validated using medications that have been tested clinically.
- A network of sites is being developed to conduct early Phase II proof-of-concept human trials. NIH will encourage the pharmaceutical industry to screen proprietary compounds in the preclinical models and, when results are positive, test them in the early Phase II human trials network. Currently quetiapine and levetiracetam are being evaluated in this network.
- Pharmacogenetic studies are ongoing to determine genetic variants that predict success for various medications.

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAAA**) (GPRA)

The Critical Need for Addiction Medications: Breakthrough discoveries in the last decade have led to a profound transformation in understanding the mechanisms and consequences of drug abuse and addiction. The current picture offers a unique opportunity for the results of NIH's collective research to be translated into new, effective pharmacotherapies that could, either by themselves or with tested behavioral treatments, help alleviate the devastating personal and societal impacts of addiction. Distinct from the process that occurs with many other diseases, medications development for

addiction suffers from minimal pharmaceutical industry involvement—likely because of real or perceived financial disincentives and stigma. Thus, despite many enticing scientific leads, we still have no medications available for stimulant, cannabis, inhalants, or polysubstance abuse, a gap that NIH is attempting to fill. Current efforts are capitalizing on a greater understanding of the neurobiology underlying addiction and of newly identified candidate systems and molecules. Several innovative treatment approaches—beyond targeting the brain's reward system—have proven feasible and are progressing to more advanced stages of research and development. Projects in this context include work on medications to diminish conditioned responses, promote new learning, and inhibit stress-induced relapse. In addition, vaccines (e.g., for nicotine, cocaine) are being developed that induce the body to produce drug-specific antibodies able to sequester drug molecules while they are still in the bloodstream and prevent them from entering the brain. Next-generation pharmaceuticals also will emerge from human genome studies uncovering novel targets for better tailoring of treatments according to a person's genes.

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**) (GPRA)

Muscle Recovery After Exercise or Injury: NIH funds a robust research portfolio on a wide range of basic, translational, and clinical research projects in skeletal muscle biology and diseases. In the past 2 years, NIH-funded scientists have published several papers on compounds that improve muscle function and endurance in animals. They hope that this new knowledge can be applied to improve treatments for certain muscle disorders, frailty, obesity, and other conditions in which exercise is known to be helpful, but not always practical. For example, researchers have identified two drugs that, in mice, seem to confer many of the healthful benefits of long-term exercise by giving the animals more fat-burning muscle and better endurance. Their discovery built on earlier, more basic research, which identified a protein that regulates several fat-burning genes in muscle cells. Other researchers, exploring the role of a protein found in immature muscle cells, discovered that creatine supplements taken by athletes play an important role in muscle repair. Elsewhere, at the University of Iowa's Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center, scientists have identified a disrupted molecular pathway that leads to fatigue after even mild physical exertion in mice with muscular dystrophy. Their study demonstrated that a signaling pathway that regulates blood vessel constriction in skeletal muscle after mild exercise is defective in mouse models for Duchenne muscular dystrophy and other myopathies. This finding may lead to treatments for the post-activity exhaustion that strikes many people who have neuromuscular disorders.

→ Kobayashi YM, et al. *Nature* 2008;456(7221):511-5. PMID: 18953332. PMCID: PMC2588643.
Narkar VA, et al. *Cell* 2008;134(3):405-15. PMID: 18674809. PMCID: PMC2706130.
O'Connor RS, et al. *J Physiol* 2008;586(Pt 12):2841-53. PMID: 18420707. PMCID: PMC2517193.
→ For more information, see http://www.nih.gov/news/research_matters/august2008/08112008mouse.htm
→ For more information, see http://www.nih.gov/news/research_matters/november2008/11032008neuromuscular.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAMS**, NCRR, NIA, NICHD, NINDS) (COE)

Molecular Therapy Centers for Cystic Fibrosis and Other Genetic Metabolic Diseases: NIH is working to develop new approaches to treating serious, chronic, genetic diseases like cystic fibrosis and mucopolysaccharidosis. For example, the Gene Therapy and Cystic Fibrosis Centers Program currently supports Molecular Therapy Centers and a Cystic Fibrosis Research and Translation Core Center. Molecular Therapy Centers provide shared resources to a group of investigators to facilitate development of molecular therapies for the treatment of cystic fibrosis and other genetic metabolic diseases, like so-called lysosomal storage disorders such as mucopolysaccharidosis I. The Cystic Fibrosis Research and Translation Core Center provides resources and supports research on many aspects of the pathogenesis and treatment of cystic fibrosis. These centers have made important strides in recent years, including the study of promising candidate therapeutics. One of these, PTC124, is designed to overcome a mutation in the cystic fibrosis gene that

otherwise yields a truncated, inactive cystic fibrosis protein. Other centers are screening libraries of compounds for other agents that might be safe and effective therapeutics for cystic fibrosis and other metabolic diseases.

→ Du M, et al. *Proc Natl Acad Sci U S A* 2008;105(6):2064-9.PMID: 18272502. PMCID: PMC2538881.
Galietta LJV, et al. *FEBS Letters* 2001;499(3):220-4. PMID: 11423120.
→ For more information, see http://www2.niddk.nih.gov/Research/ScientificAreas/GeneticGeneTherapy/GCTR.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**)

New Indications for Established Agents to Treat Chronic Disease: When identifying interventions to treat an illness or chronic condition, testing drugs that already have been developed for other conditions sometimes can be faster and more cost-effective than designing entirely new agents because drug safety profiles already have been established, and contraindications already are known. NIH intramural investigators currently are exploring the use of several established agents in the treatment of chronic disease. For example, a growing body of animal research suggests that the compound fenoterol, widely used for treatment of pulmonary disease, may be effective in the treatment of congestive heart failure. Experimental results with fenoterol are sufficiently encouraging to recommend advancing translational efforts and planning clinical trials. Other studies in animal models have shown that the drug erythropoietin, used to treat certain types of anemia, has a protective effect on the heart if administered shortly after a heart attack. Based on the results of these studies, researchers have initiated a study to assess the effects of erythropoietin (EPO) on the heart after a heart attack. Researchers also have reported preclinical data that suggest a therapeutic benefit of the diabetes drug exendin-4 in the treatment of stroke and Parkinson's disease.

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (I) (**NIA**)

Therapeutics for Rare and Neglected Diseases Program (TRND): NIH is developing a congressionally mandated therapeutics development program for rare and neglected diseases. The ORDR will handle oversight and governance of TRND, and researchers will perform TRND's laboratory work in a new facility administered by the intramural program of NHGRI. TRND will build upon the similarly structured NIH Chemical Genomics Center (NCGC). NCGC facilitates drug development from the basic research laboratory to the chemical probe stage, which is when researchers begin to lay the groundwork for intensive preclinical development of candidate drugs. Picking up where NCGC and other organizations leave off, TRND will concentrate its efforts on the preclinical stage of drug development. TRND's aim will be to move candidate drugs forward in the drug development pipeline until they meet Food and Drug Administration (FDA) requirements for an Investigational New Drug (IND) application. Once TRND generates enough data to support an IND application for a candidate drug, it will be licensed to an experienced organization outside of NIH, such as a biotechnology or pharmaceutical company, for human testing and regulatory submission. TRND also will devote considerable resources to the repositioning or repurposing of approved products for use in rare and neglected diseases. Like NCGC, TRND will pull together researchers with expertise in a broad and diverse range of scientific disciplines and disease areas. Specifically, TRND will encourage investigators from both inside and outside of NIH, from the public, private, and nonprofit sectors, to submit projects for work within its intramural facility. This will create ongoing collaborations that will benefit researchers and, most importantly, patients with rare and neglected diseases. NIH ICs and Offices have recommended staff members with expertise and experiences in product development programs to serve on a Trans-NIH Staff Advisory Group that will provide ongoing consultation regarding the operation of TRND and help integrate TRND with related or complementary efforts in the NIH ICs. A second group providing input for TRND is the External Expert Panel comprised of experts in preclinical drug development and rare and neglected diseases from academia, industry, and patient advocacy communities.

→ For more information, see http://www.genome.gov/27531965

→ For more information, see https://rarediseases.info.nih.gov/TRND/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**ODP/ORDR**, NHGRI)

Long-Term Oxygen Treatment Trial (LOTT): Although oxygen therapy is known to benefit patients who have chronic obstructive pulmonary disease (COPD) and experience severe hypoxemia when resting, its value for patients with less-serious disease is not known. In November 2006, NIH and the Centers for Medicare and Medicaid Services launched the LOTT, the largest-ever randomized clinical trial of the effectiveness and safety of long-term, home oxygen therapy for patients with COPD and moderately severe hypoxemia. Results are expected to shed light on the role of oxygen therapy in the management of such patients and provide a scientific basis for Medicare coverage decisions. The LOTT trial is the focus of a new GPRA goal—"By 2012, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia."

→ For more information, see http://www.nhlbi.nih.gov/new/press/06-11-20.htm
→ (E) (**NHLBI**) (GPRA)

Phase II Clinical Trials of Novel Therapies for Lung Diseases: Better treatments and diagnostic procedures are needed for lung diseases and sleep disorders. Although the results of basic research studies in cells, tissues, and animal models; investigations of biomarkers; and functional genomics have improved understanding of the pathogenesis of lung diseases and sleep disorders and suggested treatment targets, human testing often has not kept pace with the basic science advances. A recent solicitation encourages Phase II clinical trials to provide high-quality, proof-of-concept data to justify larger clinical efficacy trials. To foster collaborations between basic and clinical researchers and to obtain mechanistic understanding of new treatment approaches, each project is to include one interventional clinical trial led by a clinical investigator and at least one basic ancillary research study that is tightly related to the clinical question and led by a basic researcher. It is expected that four to six awards will be made in FYs 2010 and 2011.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-003.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NHLBI**)

Idiopathic Pulmonary Fibrosis Clinical Research Network: The idiopathic pulmonary fibrosis (IPF) clinical research network was established in 2005 to explore treatment of patients with newly diagnosed IPF using combinations of drugs at multiple points that could stabilize or improve the disease. The network includes 11 clinical centers (with multiple satellite sites), a data coordinating center, and a clinical research skills-development core. The first clinical trial to treat pulmonary hypertension in patients with advanced IPF was completed in September 2009, and preliminary results are expected by November 2009. Two additional protocols are to begin in fall 2009. One will test the results of a prior trial that treated IPF patients with a combination of corticosteroids, azathioprine, and n-acetylcysteine (NAC) by using a multiple-arm, double-blind, randomized trial to ascertain if the findings were the effect of NAC only. A second trial will assess the effect of oral anticoagulation therapy on the progression of fibrosis in IPF patients. Additionally, the network has enabled support of a number of new ancillary mechanistic studies that are conducted in conjunction with the main intervention trials.

→ For more information, see http://www.ipfnet.org
→ (E) (**NHLBI**)

Obstructive Sleep Apnea Treatment Trials: In 2009, NIH completed two prospective, randomized, double-blinded, sham-controlled multicenter evaluations of nasal continuous positive airway pressure (CPAP) as a first-line treatment for obstructive sleep apnea (OSA). OSA is characterized by brief episodes of airway obstruction that prevents air from

reaching the lung and disturbs sleep. It is the single most pervasive airway disorder and is associated with a greater risk of behavioral impairment, hypertension, stroke, diabetes, and all-cause mortality. The $14 million Apnea Positive Pressure Long-Term Efficacy Study (APPLES) was launched in September 2002 to determine whether CPAP therapy, compared with placebo, alleviates debilitating cognitive impairment associated with OSA. More than 1,100 OSA cases were studied over a period of 6 months using a battery of behavioral and sleep tests to assess changes in cognitive ability, mood, sleepiness, and quality of life. The $3 million CATNAP study was launched in August 2003 to assess the threshold of OSA severity at which CPAP therapy improves sleep-related functional and medical outcomes. It studied 200 cases of mild OSA in which participants exhibited significant sleepiness. Findings from APPLES and CATNAP that are to be reported in 2010 will be the first evidence from U.S.-based clinical trials to guide health care providers in determining who should be evaluated and treated and what behavioral benefits can be expected.

- → Kushida CA, et al. *J Clin Sleep Med* 2006;2(3):288-300. PMID: 17561541.
  Saboisky JP, *Expert Opin Ther Targets* 2009;13(7):795-809. PMID: 19530985. PMCID: PMC2729816.
  Calvin AD, et al. *Metab Syndr Relat Disord.* 2009;7(4):271-8. PMID: 19344228.
- → For more information, see https://apples.stanford.edu
- → This example also appears in Chapter 3: *Clinical and Translational Research*
- → (E) (**NHLBI**)

Action to Control Cardiovascular Risk in Diabetes (ACCORD): ACCORD is a multicenter randomized clinical trial of 10,251 persons with type 2 diabetes who are at high risk of a cardiovascular disease (CVD) event. It was designed to assess whether the rate of major CVD events could be reduced by intensive control of blood sugar (glycemia) compared with the current standard of care, intensive control of blood pressure compared with the current standard of care, or treatment of blood lipids with fibrate plus statins compared with treatment with statins alone. On February 6, 2008, NIH announced that participants receiving intensive glycemia treatment would be transitioned to the ACCORD standard treatment approach because higher mortality was observed among them. The glycemia main results were published in the *New England Journal of Medicine* in June 2008. They have substantial implications for the clinical treatment of diabetes, especially in older patients at high risk of CVD. The blood pressure and lipid trials are continuing as designed, with the last patient visits completed in June 2009.

- → Action to Control Cardiovascular Risk in Diabetes Study Group, et al. *N Engl J Med* 2008;358(24):2545-59. PMID: 18539917.
- → For more information, see http://clinicaltrials.gov/ct2/show/
- → For more information, see http://www.accordtrial.org
- → This example also appears in Chapter 3: *Clinical and Translational Research*
- → (E) (**NHLBI**, CDC, NEI, NIA, NIDDK)

Comparative Effectiveness Study Finds Laser Treatment Preferable in Diabetic Macular Edema: The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network dedicated to conducting multicenter clinical research for diabetic retinopathy and associated conditions. The DRCR.net was formed in September 2002 and currently includes 199 participating sites with more than 670 physicians throughout the United States. About 45 percent of the 18 million Americans diagnosed with diabetes have visual disorders such as macular edema. This occurs when the central part of the retina called the macula swells in diabetics—possibly leading to blindness. Laser treatment to reduce swelling has been the standard of care. However, early reports of success in treating diabetic macular edema with a corticosteroid, triamcinolone, have led to its widespread use. A DRCR clinical trial found that laser therapy is more effective and has far fewer side effects than intraocular injections of triamcinolone in treating diabetic macular edema. In the corticosteroid-treated group, 28 percent experienced substantial vision loss as compared to 19 percent in the laser-treated group. Surprisingly and unexpectedly, vision improved in about one-third of the eyes treated with laser therapy. Results of this study confirm the preferential use of laser treatment for diabetic macular edema.

→ Diabetic Retinopathy Clinical Research Network, et al. *Ophthalmology* 2007;114(10):1860-7. PMID: 17698196. PMCID: PMC2245885.
→ For more information, see http://public.drcr.net/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NEI**)

Promising Clinical Trials of Gene Transfer for Severe Childhood Eye Disease: Leber congenital amaurosis (LCA) is an early-onset, severe retinal disease that results from mutations in any 1 of 13 genes. One form of LCA results from mutations in a gene called RPE65. In 1993, NIH intramural scientists discovered that RPE65 plays a key role in the visual cycle, the set of biochemical interactions that converts light into an electrical signal to initiate vision. Mutations in RPE65 were found to disrupt the visual cycle, resulting in LCA and blindness. Retinal cells in children with LCA remain viable for several years, providing a window of opportunity to intervene therapeutically. An NIH-supported Phase I clinical trial of RPE65 gene transfer in LCA found the treatment is safe and that visual function improved. Two other independent Phase I clinical trials of RPE65 gene transfer also found evidence of visual improvement, but further work is needed to develop the therapeutic potential fully. Ongoing studies are exploring the range of therapeutic doses in adult and adolescent patients as well as rigorous evaluation of the effectiveness of this treatment. Gene transfer is particularly well-suited to the treatment of eye disease. This clinical trial is an important step in treating LCA and in establishing proof-of-concept for gene transfer as a viable therapy for eye disease.

→ Cideciyan AV, et al. *Proc Natl Acad Sci U S A* 2008;30;105(39):15112-7. PMID: 18809924. PMCID: PMC2567501.
→ For more information, see http://www.pnas.org/content/105/39/15112.long
→ For more information, see http://www.nei.nih.gov/lca/
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NEI**)

Look AHEAD (Action for Health in Diabetes): This NIH-led, multicenter, randomized clinical trial is examining the long-term health effects of an intensive lifestyle intervention (ILI) designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity. The study enrolled more than 5,100 overweight or obese adults with type 2 diabetes. Results from the first year of the study showed that participants in the ILI group achieved clinically significant weight loss; this was the case across all subgroups of the ethnically and demographically diverse study population. In addition, this weight loss was associated with an increase in "health-related quality of life" and improved cardiovascular fitness, blood pressure, cholesterol, and blood glucose, as compared to a control group receiving diabetes support and education. As another major point for health outcome measurement, the study recently completed 4 years of intervention and follow-up. In the coming years, continued follow-up of the Look AHEAD participants will show whether the ILI can reduce the incidence of heart attack and stroke and improve other health-related outcomes in this population. These findings will have important implications for treating type 2 diabetes.

→ For more information, see http://www2.niddk.nih.gov/Research/ClinicalResearch/ClinicalTrials/Patients/ClinicalResearchLookahead.htm
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIDDK**, CDC, NCMHD, NHLBI, NINR, ORWH) (GPRA)

Following up on the Multimodal Treatment Study of Children with ADHD (MTA): Children with attention deficit hyperactivity disorder (ADHD), the most common of the psychiatric disorders that appear in childhood, often raise great concern from their parents and teachers because of their inability to focus on or finish tasks. Over time, these children may develop other emotional problems, including mood disorders, loss of self-esteem, and substance abuse. To address these issues, NIH is sponsoring an ongoing, multisite, follow-up of children from the MTA study—a treatment trial of nearly

600 ADHD-diagnosed elementary school children. Findings from the original MTA showed that long-term combination treatment (medication and psychosocial/behavioral treatment), as well as medication-management alone, significantly were superior to intensive behavioral treatments and routine community care in reducing ADHD symptoms. In the follow-up study (n = 485 10 to 13 year olds), children from this cohort and others who received similar pharmacotherapy were assessed for substance abuse outcomes. The study found that despite treatment, children with ADHD showed significantly higher rates of delinquency and substance abuse. Follow-up of the MTA sample is continuing as the participating children go through adolescence and enter adulthood.

→ Molina BS, et al. *J Am Acad Child Adolesc Psychiatry* 2009;48(5):484-500. PMID: 19318991.
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0028.html
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0029.html
→ For more information, see http://www.nida.nih.gov/ResearchReports/comorbidity/
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIDA**, NIMH)

Functional Gastrointestinal (GI) Disorders: NIH is leading a number of initiatives to improve the diagnosis and treatment of functional GI disorders. The Gastroparesis Clinical Research Consortium (GpCRC) performs clinical, epidemiological, and therapeutic research to improve treatment of patients with gastroparesis (inability to move food properly from the stomach through the digestive system). Ongoing GpCRC studies include the Gastroparesis Registry and a multicenter, randomized clinical trial testing the use of nortriptyline (a tricyclic antidepressant) for treatment of gastroparesis. The use of antidepressants for the treatment of functional dyspepsia (indigestion) is being tested in the Functional Dyspepsia Treatment Trial; the study also aims to identify genetic markers associated with improved treatment outcomes. Additional NIH-sponsored clinical studies are testing the benefit of short-term cognitive-behavioral treatment for irritable bowel syndrome (IBS) and evaluating methods for diagnosing and treating Sphincter of Oddi Dysfunction, a disorder that results in bouts of abdominal pain from spasms of biliary and pancreatic valves. In addition, NIH provides continued support for the Center for Neurovisceral Sciences and Women's Health at UCLA, which conducts basic and clinical research on how the brain and digestive system communicate and how alterations in this communication result in IBS and other disorders. These initiatives will reduce the physical and psychosocial burdens associated with functional GI disorders.

→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00398801
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00765895
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00248651
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00738920
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00688662
→ For more information, see http://www.cns.med.ucla.edu
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**, NCCAM, ORWH)

Improving the Lives of Asthmatic Children in the Inner City: The NIH Inner-City Asthma Consortium (ICAC) of 10 academic clinical centers, launched in 2002, evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. The Consortium also pursues studies to understand mechanisms underlying the onset and progression of asthma and research to develop diagnostic and prognostic biomarkers. An ICAC longitudinal birth cohort study involving 500 inner-city children is investigating the immunologic causes of the development of recurrent wheezing, which can be indicative of asthma in children under age 3. ICAC has extended the study to follow all participant children to age 7, when the diagnosis of asthma can be definitive. Researchers hope to identify immunologic characteristics that will predict the development and severity of asthma at a later age. ICAC researchers are conducting two clinical trials to determine the safety, dosing levels, and biologic activity of a potential new allergy immunotherapy for cockroach allergen, which ICAC studies previously found to be a major determinant of asthma

severity among inner-city children. Finally, an ICAC clinical trial assessed the benefit of using exhaled nitric oxide (NO) as a marker for asthma management. Although the study reinforced the importance of the NIH asthma guidelines for disease control, it did not find that measuring exhaled NO provided any additional clinical benefit.

→ Szefler SJ, et al. *Lancet* 2008;372(9643):1065-72. PMID: 18805335. PMCID: PMC2610850.
→ For more information, see http://www3.niaid.nih.gov/topics/asthma/research/researchActivities.htm
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAID**)

Liver Disease Research: NIH supports clinical research to address the spectrum of liver diseases. The Nonalcoholic Steatohepatitis Clinical Research Network conducts placebo-controlled clinical trials of treatments for this condition, both in adults given pioglitazone or vitamin E, and in children given metformin or vitamin E. The Hepatitis B Clinical Research Network will conduct clinical trials to evaluate the effectiveness of different treatments and learn more about the natural history of this disease. The Childhood Liver Disease Research and Education Network combines and expands previous consortia focused on biliary atresia and cholestatic liver disease. This new network will foster discovery of new diagnostic and treatment options for children with these diseases or who undergo liver transplantation, and support research training in rare pediatric liver diseases. Plans for another clinical network are beginning with a study to test whether immunosuppression minimization would be safe and thus beneficial in children several years after liver transplantation. The adult and pediatric Acute Liver Failure Study Groups address the problem of acute liver failure due to drugs or other factors. Current studies are testing potential therapies to improve survival. For example, results of a clinical trial to test intravenous N-acetylcysteine as a treatment for nonacetaminophen-related acute liver failure showed significant improvement in transplant-free survival in individuals who received therapy early in the course of their acute liver failure. The Drug-Induced Liver Injury Network conducts research aimed at understanding, diagnosing, and ultimately preventing liver toxicity due to drugs or complementary and alternative medicines. Future efforts of this network will focus on identifying genetic risk factors for drug-induced liver toxicity.

→ Lee WM, et al. *Gastroenterology* 2009;137(3):856-64, 864.e1. PMID: 19524577.
→ For more information, see http://www.jhucct.com/nash/
→ For more information, see http://dilin.dcri.duke.edu/
→ For more information, see http://www.utsouthwestern.edu/utsw/cda/dept25203/files/89624.html
→ For more information, see http://www.palfstudy.org/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**, FDA, NCI, NICHD) (GPRA)

Pelvic Floor Disorders: Research supported by NIH showed that nearly one-quarter of all U.S. women were afflicted with one or more pelvic floor disorders. These disorders result when the muscles and connective tissue within the pelvic cavity weaken or are injured, leading to dysfunction of one or more pelvic organs. The NIH-supported Pelvic Floor Disorders Network, with seven sites throughout the country, supports research on the prevention and treatment of pelvic floor disorders. A recent study by the network revealed that a special two-step surgical procedure, compared to standard practice, reduced by half the incidence of urinary incontinence in women with pelvic organ prolapse. In addition, NIH plans to enhance collaborative research among basic scientists and clinician researchers in female pelvic floor disorders, to promote research that has the greatest clinical applicability for addressing unknown aspects of physiology and pathophysiology of pelvic function.

→ For more information, see http://www.pfdnetwork.org/
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-008.html
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NICHD**, NIDDK, ORWH)

Urology Research: The Urinary Incontinence Treatment Network (UITN) conducts long-term studies and clinical trials of the most commonly used surgical, pharmacological, and behavioral approaches for management of urinary incontinence in women diagnosed with stress and mixed incontinence. Recently, a different group of investigators completed the Program to Reduce Incontinence by Diet and Exercise (PRIDE) study and determined that a weight loss program could reduce significantly the frequency of urinary incontinence in overweight and obese women. Several studies address interstitial cystitis/painful bladder syndrome (IC/PBS), a urologic condition whose prevalence is uncertain and which remains difficult to diagnose and treat. The RAND Interstitial Cystitis Epidemiology (RICE) study is designed to estimate the prevalence of interstitial cystitis and establish a working definition of this condition. The Boston Area Community Health (BACH) Survey is a population-based study of urologic conditions, including IC/PBS, in more than 5,500 adults. Results emerging from BACH about IC/PBS will provide a clearer picture on the IC/PBS burden in the population, and will inform research efforts to reverse this burden. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is designed to enhance understanding of the major urological chronic pelvic pain disorders, including IC/PBS and chronic prostatitis/chronic pelvic pain syndrome.

→ Burgio KL, et al. *Ann Int Med* 2008;149:161-9. PMID: 18678843.
Subak LL, et al. *N Eng J Med* 2009;360(5):481-90. PMID: 19179316.
→ For more information, see http://www.uitn.net/
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**, NICHD)

Chemical Messengers in the Brain Determine the Response to Stress and Regulate Craving For Alcohol: Stress contributes to many disease states, including alcohol dependence. As alcohol dependence evolves, stress systems in the brain play an increasing role in continued alcohol use and relapse. Furthermore, individuals differ widely in response to stress. NIH researchers have investigated specific chemical messengers in the brain and the roles these messengers play as mediators of behavioral stress responses and their contributions to alcohol dependence. For example, the chemical messenger neuropeptide Y (NPY) is expressed in regions of the brain implicated in arousal and in determining emotional states. Production of NPY increases in these brain regions in response to emotionally charged and stressful conditions. Higher levels of NPY are associated with lower levels of alcohol consumption. NIH researchers also have made progress in studies of another brain messenger involved in stress responses, Neurokinin 1 (NK1) and its receptor (NK1R). In a clinical study, alcohol-dependent inpatients who recently stopped drinking were treated with a drug that blocks the actions of NK1R. Patients treated with the NK1R blocker exhibited reduced alcohol cravings, improved overall well-being, and reduced blood levels of stress hormones. Brain imaging during responses to stimulation that increases the likelihood of drinking showed a beneficial effect by the drug, suggesting that such drugs could reduce relapse in alcohol-dependent individuals.

→ Zhou Z, et al. *Nature* 2008;452(7190):997-1001. PMID: 18385673. PMCID: PMC2715959.
George DT, et al. *Science* 2008; 319(5869):1536-9. PMID: 18276852.
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E/I) (**NIAAA**)

Research on Bariatric Surgery: The multicenter NIH-funded Longitudinal Assessment of Bariatric Surgery (LABS) consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Results from this study have been published in the *New England Journal of Medicine*. The study also addresses comparative effectiveness with respect to its collection of data on surgical procedures and pre- and post-operative information. Because bariatric surgery also is used in clinical practice sometimes as a treatment for severely obese adolescents, NIH additionally is supporting an observational study of teens already scheduled for surgery, Teen-LABS, to collect data to help determine whether it is an appropriate treatment option for extremely obese adolescents. A pilot study also is being conducted using the new Metabolic Clinical Research Unit at the NIH CC to examine changes in insulin resistance after

bariatric surgery. To further explore the observation that certain bariatric surgical procedures are associated with amelioration of obesity-related insulin resistance and diabetes soon after surgery, and thus independent of weight loss, NIH issued a funding opportunity announcement to encourage research in this area.

- → Adams TD, et al. *N Engl J Med* 2007;357(8):753-61. PMID: 17715409.
  The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. *N Engl J Med* 2009;316(5):445-54. PMID: 19641201.
- → For more information, see http://win.niddk.nih.gov/publications/labs.htm
- → For more information, see http://www.nih.gov/news/pr/apr2007/niddk-16.htm
- → This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Clinical and Translational Research*
- → (E/I) (**NIDDK**, ORWH)

Research Training for Clinicians in Practice-Based Research Networks Yields Results: When NIH awarded 6 7-year grants to establish 3 dental practice-based research networks (PBRNs), its aim was to assemble teams of practicing dentists to investigate with greater scientific rigor “everyday” issues in the delivery of oral health care. The impetus behind the networks was the frequent lack of research data to guide treatment decisions in the dentist's office. One of the key objectives to accomplishing the goal is providing the participating clinicians, many of whom have had no previous research experience, with the training and education needed to conduct clinical research effectively. The PBRNs have developed multiple methods of delivering research training to practicing clinicians, including training in research methods, protection of human participants, good clinical practice, research protocol development, and interpretation of research results. Descriptions of the training programs have been reported in national journals, and a collaboratively written chapter recently was accepted for publication in a textbook on PBRNs. The real proof of the value of research training, of course, is whether research relevant to clinical practice is occurring—yes it is. Over the course of the grant period, the networks each will complete approximately 15 to 20 short studies. In early 2009 almost 90 study concepts had been approved, more than 20 were underway, and several had been completed and reported. The citations below are limited to those that deal with research training.

- → DeRouen TA, et al. *J Am Dent Assoc* 2008;139(3):339-45. PMID: 18310739.
  Gilbert GH, et al. *J Am Dent Assoc* 2008;139(1):74-81. PMID: 18167389.
- → For more information, see http://www.nidcr.nih.gov/Research/DER/ClinicalResearch/DentalPracticeBasedResearchNetworks.htm
- → This example also appears in Chapter 3: *Clinical and Translational Research*
- → (E) (**NIDCR**)

End-Stage Renal Disease: According to the United States Renal Data System—an NIH-supported national data system that collects, analyzes, and distributes information about people with kidney failure—more than one-half million Americans suffer from kidney failure. Patients with this condition—known as end-stage renal disease or ESRD—require a kidney transplant or hemodialysis, a process that uses a machine to remove waste products and excess fluid from the bloodstream. To facilitate hemodialysis, some patients undergo a surgical procedure to create a site on the body that allows easy, repeated access to the blood vessels. However, over time, many vascular access sites become unusable and fail. The NIH-supported Dialysis Access Consortium found that treatment with an anti-blood clotting drug did not improve the long-term suitability of a type of access known as a fistula. A separate study by the consortium found that the long-term usability of a different type of access site, known as a graft, could be improved through treatment with a combination of aspirin and another anti-clotting drug. Still, important questions remain. To better understand the underlying biology of access site maturation, NIH is launching a Vascular Biology of Hemodialysis Vascular Access Consortium to study the molecular and cellular pathways that contribute to vascular injury and high rates of vascular access failure. Such research may inform new strategies to improve outcomes in patients undergoing hemodialysis.

→ Dember LM, et al. *JAMA* 2008;299(18):2164-71. PMID: 18477783.
Dixon BS, et al. *New Engl J Med* 2009;360(21):2191-201. PMID: 19458364.
→ For more information, see http://www.usrds.org
→ For more information, see http://www.nih.gov/news/health/may2008/niddk-22a.htm
→ For more information, see http://www.nih.gov/news/health/may2009/niddk-20.htm
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIDDK**)

Using the Web to Broaden the Delivery of Effective Treatments: NIH is testing the efficacy of delivering evidence-based psychosocial interventions for drug abuse and HIV prevention via the Web or other computer-based media, while assessing their relative cost and efficacy compared to more traditional delivery formats. Variables of interest include abstinence, treatment retention, health risk, quality of life, and social outcomes. New research shows that computer-based training for cognitive behavioral therapy appears to have both short-term and enduring effects on drug use—that is, fewer days of drug use for many months following treatment compared to controls. Another computer-based intervention, called Positive Choice, was tested in HIV-positive patients as a means of reducing risky behaviors that lead to HIV spread. Five San Francisco clinics participated, exposing patients to a "video doctor" to conduct a risk assessment and risk reduction counseling program. Patients waiting to see the provider use a laptop computer to watch video clips and respond by means of a color-coded keyboard. That, too, was successful, and sharply reduced sexual and drug risk behaviors in HIV-positive patients. These delivery methods stand not only to greatly increase cost effectiveness of interventions, but to provide a means for broader dissemination, including to those in remote locations where therapists may not be available. Our research will continue to investigate how such interactive technology can be integrated to improve the addiction treatment system and bring about more widespread adoption of evidence-based approaches.

→ For more information, see http://ajp.psychiatryonline.org/cgi/content/full/165/7/
→ For more information, see http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0001988
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIDA**)

Asthma Exacerbations: In FY 2005, NIH began a basic and clinical research initiative to improve understanding of the causes of asthma exacerbations and to facilitate the development of more effective treatments to control asthma symptoms. Twelve projects have been funded under this initiative. NIH is assessing the progress of the initiative through an ongoing GPRA goal—"to identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating exacerbations, by 2014."

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-04-029.html
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NHLBI**) (GPRA)

Acute Kidney Injury: Acute kidney injury (also called "acute renal failure") is a serious medical condition characterized by a relatively rapid loss of kidney function, resulting in an inability to excrete waste products and excess fluid and salts. It is a common complication in hospitalized patients, and mortality rates approach 50 percent among the critically ill. There is no effective drug treatment, so physicians rely on hemodialysis and other forms of life-sustaining kidney replacement therapy. Some earlier, small studies suggested that increased frequency or intensity of hemodialysis might improve survival in patients with acute kidney injury. The NIH-funded Acute Renal Failure Trial Network (ATN) Study enrolled more than 1,100 critically ill patients with acute kidney injury as well as failure of at least one additional organ or a serious infection (sepsis). It found no significant difference in death rates after 60 days between patients treated with conventional dialysis and those who received a more intensive dialysis regimen. These findings may spare patients from unnecessarily intensive medical interventions, and also underscore the need for research into other approaches to treating acute kidney injury. NIH recently launched a Natural History of Acute Kidney Injury study—ASSESS AKI—to identify and validate

biomarkers and risk assessment tools for kidney function, injury, and recovery in patients with acute kidney injury; a subset of this study will focus on pediatric patients.

→ The VA/NIH Acute Renal Failure Trial Network, et al. New Engl J Med 2008:359(1):7-20. PMID: 18492867. PMCID: 2574780.
→ For more information, see http://www.nih.gov/news/health/may2008/niddk-22.htm
→ (E) (**NIDDK**)

Comparative Effectiveness Study of Drugs for Age-Related Macular Degeneration: Lucentis was approved by FDA in 2006 for treatment of advanced age-related macular degeneration (AMD), a leading cause of vision loss in older Americans. Though the drug is safe and effective, it is expensive—approximately $2,000 per month—and repeated injections are required. Avastin is a similar pharmaceutical but is far less expensive—approximately $100 per month—and also has been used extensively in treating patients with AMD. Most retinal specialists think that Avastin is a safe and effective alternative to Lucentis. To resolve this question, NIH is funding the Comparison of AMD Treatments Trial (CATT), a multicenter, randomized, clinical trial to compare the safety and efficacy of Avastin and Lucentis, and to explore less-frequent treatment schedules for both drugs. The first participants were randomized in early 2008. If Avastin proves to be comparable to Lucentis, the cost savings could reach $2-3 billion per year. Less frequent treatment schedules also would lower costs, reduce treatment risk, and improve patient quality-of-life.

→ For more information, see http://www.nei.nih.gov/news/pressreleases/022208.asp
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NEI**)

BARI 2D Clinical Trial: Cardiovascular disease (CVD) is the leading cause of diabetes-related deaths—about 65 percent of people with diabetes die of heart disease or stroke. Recognizing the importance of comparative effectiveness research, NIH in FY 2000 awarded support for the BARI 2D clinical trial to evaluate management strategies for patients with stable coronary artery disease and type 2 diabetes. Its goal was to determine whether mortality and CVD event rates could be reduced by early coronary revascularization and intensive medical therapy compared with intensive medical therapy alone, and by an initial strategy of insulin sensitization compared with provision of insulin to treat hyperglycemia. The trial found that neither early revascularization nor insulin sensitization was superior to the tested alternatives in terms of CVD event rates. However, among patients for whom bypass surgery was deemed to be the appropriate revascularization procedure, prompt revascularization reduced the rate of major, nonfatal CVD events such as heart attack and stroke.

→ BARI 2D Study Group, et al. *N Engl J Med* 2009;360(24):2503-15. PMID: 19502645.
→ For more information, see http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?
→ For more information, see http://content.nejm.org/cgi/reprint/360/24/2503.pdf
→ For more information, see http://content.nejm.org/cgi/reprint/360/24/2570.pdf
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NHLBI**, NIDDK)

Improving Transplantation Outcomes: Organ transplantation prolongs survival and greatly improves quality of life for children and adults suffering from a wide range of congenital and acquired diseases. Yet, despite advances in transplantation, normal life expectancy and health-related quality of life are not restored fully by organ transplantation. To improve the outcomes of organ transplantation, NIH supports the Clinical Trials in Organ Transplantation (CTOT) initiative, a cooperative, multisite consortium to develop and implement interventional and observational clinical studies, accompanied by mechanistic studies.

In one notable CTOT study, NIH-supported investigators developed a regimen that included transplantation of both kidney and bone marrow from the same donor and use of immunosuppressive therapies prior to and just after transplantation. Nine to 14 months after the transplant, investigators were able to discontinue all immunosuppressive medications with this regimen in four of the five patients, without subsequent rejection of the kidney. In another study, NIH-supported investigators studied whether acute graft rejection was associated with changes in the expression of genes involved with the adaptive immune response. They measured levels of microRNAs in healthy transplanted kidneys and in transplants undergoing rejection. The team found a pattern of six microRNAs that could distinguish healthy kidneys from those in the process of being rejected. These results suggest that microRNAs may be a useful measurement for assessing human kidney transplant status. If the rejection signature appears early enough, doctors one day may be able to treat patients before organ damage occurs and to better tailor immunosuppressive therapy to the individual patient.

→ Kawai T, et al. *N Engl J Med* 2008 Jan 24;358(4):353-61. PMID: 18216355. PMCID: PMC2819046.
→ For more information, see http://www.immunetolerance.org/
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIAID**, NHLBI, NIDDK)

Progress Toward Immune Tolerance: Since 1999, NIH, with its cosponsor the Juvenile Diabetes Research Foundation International, has supported the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. The ITN is pioneering novel strategies for studying and testing new drugs and therapies against autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based upon principles of immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to “reeducate” the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. To understand the underlying mechanisms of action of the candidate therapies and to monitor tolerance, the ITN has established state-of-the art core laboratory facilities to conduct integrated mechanistic studies, and to develop and evaluate markers and assays to measure the induction, maintenance, and loss of tolerance in humans. Current ITN studies include pancreatic islet transplantation for type 1 diabetes; approaches to slow or reverse progression of autoimmune diseases such as type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus and other rheumatologic disorders; approaches to treat and prevent asthma and allergic disorders, including food allergy; and therapies to prevent liver and kidney transplant rejection without using lifelong immunosuppressive drugs.

→ For more information, see http://www.immunetolerance.org/
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAID**, NIDDK)

Unexpectedly, Corneas from Older Donors Found Suitable for Transplantation: Light first enters the eye through the crystal clear cornea and is focused on the retina. Each year approximately 33,000 Americans undergo corneal transplants to replace diseased corneas that either become cloudy or no longer properly focus light, causing severe visual impairment. Corneal transplants are among the most common and successful transplantation procedures in medicine. Availability of donor tissue is key to this sight-restoring procedure. However, many eye banks refrain from harvesting tissue from donors over age 65 because of uncertainty about the integrity of older corneas. Newly instituted FDA regulations to further safeguard transplant recipients and the common use of LASIK surgery to correct refractive errors—which renders corneal tissue unusable for transplantation—could significantly limit future tissue supplies. The Cornea Donor Study (CDS) found that corneal transplants using tissue from donors ages 66-75 have similar success rates to those using tissue from donors ages 12-65. Based on these findings, the study authors recommend that the age limit for donor tissue could be safely expanded to age 75. The CDS study gives eye banks, transplant surgeons, and patients confidence in the use of older donor tissue, and should help eye banks keep pace with the demand for corneal tissue.

→ Cornea Donor Study Investigator Group, et al. *Ophthalmology* 2008;115(4):620-626.e6. PMID: 18387407.
→ For more information, see http://www.ophsource.org/periodicals/ophtha/article/PIIS0161642008000055/fulltext

→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NEI**)

According to a Government Survey, 38 Percent of Adults and 12 Percent of Children Use Complementary and Alternative Medicine: In December 2008, NIH and the National Center for Health Statistics released new findings on Americans' use of complementary and alternative medicine (CAM). The findings are from the 2007 National Health Interview Survey (NHIS), an annual in-person survey of Americans regarding their health- and illness-related experiences. According to the survey, approximately 38 percent of adults and nearly 12 percent of children use some form of CAM. For both adults and children, the most commonly used type of CAM is nonvitamin/nonmineral natural products, and the most common use for CAM is to treat pain. Although overall use of CAM among adults has remained relatively stable since 2002 (the last time NHIS included a CAM section), the use of some specific CAM therapies has varied substantially; for example, deep breathing, meditation, massage therapy, and yoga have all shown significant increases. The 2007 NHIS was the first to ask about CAM use by children. The NHIS also reports on characteristics of CAM users, such as gender, age, education, geographic region, poverty status, and health indicators. The 2007 NHIS provides the most current, comprehensive, and reliable source of information on Americans' use of CAM. These statistics confirm that CAM practices are a frequently used component of American's health care regimens, and reinforce the need for rigorous research to study the safety and effectiveness of these therapies. The data also point out the need for patients and health care providers to openly discuss CAM use to ensure safe and coordinated care. Future analyses of these data may help explain some of the observed variation in the use of individual CAM therapies and provide greater insights into CAM use patterns among Americans.

→ Barnes PM, et al. *Natl Health Stat Report* 2008;(12):1-23. PMID: 19361005.
→ For more information, see http://www.cdc.gov/nchs/data/nhsr/nhsr012.pdf
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NCCAM**, CDC)

Glucosamine and Chondroitin Fare No Better Than Placebo in Slowing Structural Damage of Knee Osteoarthritis: Osteoarthritis affects an estimated 27 million Americans, and researchers are seeking ways not only to treat pain, but also to address the loss of cartilage—a hallmark of the condition. The two-part Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), funded by NIH, investigated whether this dietary supplement can treat pain and diminish structural damage associated with knee osteoarthritis. In the primary study (GAIT I), combined glucosamine/chondroitin sulfate did not provide significant relief among study participants overall, although a smaller subgroup with moderate to severe pain did show significant relief. The 18-month GAIT II ancillary study followed cartilage loss in GAIT participants with moderate or severe osteoarthritis in one or both knees, comparing the effects of glucosamine and/or chondroitin sulfate with placebo. In GAIT II, glucosamine and chondroitin—together or alone—appeared to fare no better than a placebo in slowing loss of cartilage in osteoarthritis of the knee, measured by joint space width as seen on x-rays. Interpreting the study results is complicated, however, because participants taking placebo had a smaller loss of cartilage than predicted. In addition to its findings on the effects of dietary supplements taken by many Americans for osteoarthritis, GAIT II provided new insights on osteoarthritis progression, techniques for measuring loss of joint space width, and characteristics of osteoarthritis patients who may respond best to glucosamine/chondroitin.

→ Sawitzke AD, et al. *Arthritis Rheum* 2008;58(10):3183-91. PMID: 18821708.
→ For more information, see http://nccam.nih.gov/news/2008/092908.htm
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NCCAM, NIAMS**)

Half of Surveyed Physicians Use Placebo Treatments for Patients: Treating patients with placebos has a long, complicated, and often controversial history. Nonetheless, little actually is known about U.S. physicians' current attitudes toward and use of placebo treatments. A national survey funded in part by NIH looked at placebo-prescribing practices among 679 internists and rheumatologists—specialties that commonly treat patients with debilitating chronic conditions. The survey found that about half of the physician respondents prescribed placebo treatments on a regular basis. Most (62%) said they think the practice is ethical. Among physicians who prescribed placebos, few said they used inert treatments such as saline injections or sugar pills; they were more likely to recommend over-the-counter analgesics (41%) or vitamins (38%), and some used antibiotics (13%) or sedatives (13%) as placebos. The survey also found that the physicians who used placebos rarely described them as such to patients. Instead, physicians most commonly described the treatments as medicine that typically is not used for the patient's condition but that might be beneficial. The survey provides insights into the complex relationship between placebo use and physicians' traditional role in promoting positive expectations in their patients. It also raises concerns about the use of "active" placebos, particularly antibiotics and sedatives, when they are not medically indicated. Prescribing placebo treatments remains an appropriate topic for ethical and policy debates.

→ Tilburt JC, et al. *BMJ* 2008 Oct 23;337:a1938. PMID: 18948346. PMCID: PMC2572204.
→ For more information, see http://nccam.nih.gov/research/results/spotlight/102408.htm
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NCCAM**)

Building a Longitudinal Mental Health Tracking System: NIH has laid the initial groundwork to develop a mental health tracking system that will provide epidemiologic information on mental disorders on a continuing basis. By working with Federal agencies that currently conduct large-scale, ongoing national surveys, and adding detailed measures of mental health status, functioning, and service use, NIH will leverage existing resources to collect important mental health information in a cost-efficient manner. The longitudinal nature of the resulting data will provide NIH the ability to track the prevalence, incidence, severity, correlates, and trajectories of mental disorders, as well as related service use and outcomes, over time. The resulting data also could provide important information on key subgroups (e.g., racial/ethnic populations, people with autism) and geographic areas of varying sizes (e.g., states, counties). These data are critical for targeting future research activities and ensuring the effectiveness of delivered interventions.

→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIMH**)

Advances in Mental Health Treatment Development: NIH continues to fund research into the development of targeted medications and treatments for mental disorders.

- *Novel NeuroAIDS Therapies:* Integrated Preclinical/Clinical Program (IPCP): The IPCP supports drug development efforts focused on new targets that may modulate immune responses and protect brain cells in the context of HIV infection. One NIH-supported group will develop the use of nanotechnology to enhance delivery of HIV drugs to the brain. Another research group will investigate the therapeutic potential of various compounds to treat or prevent HIV-associated mental disorders.
- *Innovative Approaches to Personalizing the Treatment of Depression:* NIH will advance research on individualizing the treatment of depression by supporting efforts to develop models and test new approaches that, by accounting for patient characteristics, aim to be more specific and thus potentially lead to more effective and efficient treatment interventions. Several studies will be supported through this initiative.
- *Fast-acting Depression Treatments:* Previous NIH-funded research found that ketamine can lift depression in just hours, instead of the weeks it takes conventional antidepressants. NIH researchers now have identified a marker that predicts a patient's response using the split-second accuracy of magentoencephalography. Depressed patients showed

increased activity in the anterior cingulate cortex (ACC; a region found in brain imaging studies to signal better treatment responsiveness) that correlated with their response to ketamine while viewing certain visual stimuli. This ACC activity may indicate the dysfunctional workings of the brain circuit that is targeted by ketamine.

→ Salvadore G, et al. *Biol Psychiatry* 2009;65(4):289-95. PMID: 18822408. PMCID: PMC2643469.
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-040.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-010.html
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIMH**)

Clinical Trials Networks for the Treatment of Mental Disorders: NIH is using its extensive clinical trials networks as platforms for investigating effective treatments for mental disorders. The networks, which are maintained through infrastructure supported by NIH, evolved from a recent series of practical clinical trials. The networks comprise more than 60 sites throughout the United States that maintain continual outreach efforts to diverse groups of patients and families with mental illnesses. The Bipolar Trials Network is conducting the Lithium Use for Bipolar Disorder (LiTMUS) trial, which will study the use of moderate-dose lithium for the treatment of bipolar disorder among 264 participants. The Depression Trials Network is seeking participants for the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. This study will examine for the first time whether two different medications, when given in combination as the first treatment step, compared to one medication, will enhance remission rates, increase speed of remission, be tolerable to the participant, and provide better sustained benefits in the longer term. Results of this study, involving 660 participants, will inform practitioners in managing the treatment of patients with chronic or recurrent depression.

→ For more information, see http://www.clinicaltrials.gov/show/NCT00667745
→ For more information, see http://www.clinicaltrials.gov/show/NCT00590863
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIMH**)

Recovery After an Initial Schizophrenic Episode (RAISE): Significant impairment of social and vocational function is the norm in chronic schizophrenia, and while antipsychotic drugs remain effective, they are not able to restore skills and abilities lost to the illness. A person experiencing an initial psychotic episode usually responds well to antipsychotics and, unlike chronically ill patients, may recover completely from that first episode. NIH will fund an initiative to determine whether function could be preserved and disability forestalled after an initial schizophrenic episode with an intense and sustained pharmacological, psychosocial, and rehabilitative intervention. A single project will be supported to: (1) test the feasibility of recruiting and retaining newly diagnosed patients in a longitudinal trial; (2) develop the treatment model—a mix of pharmacological, psychological, and rehabilitative interventions—that is most likely to preserve function and maintain patient participation; and (3) determine the nature of the control intervention. This initiative will set the stage for a large-scale, definitive, randomized clinical trial.

→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIMH**) (ARRA)

Addressing Pain and Palliative Care in Chronic Diseases

Understanding the Roles of Non-Neuronal Cells in Neuropathic Pain Provides New Targets for Intervention: Chronic pain caused by nerve injury, called neuropathic pain, is difficult to treat because we do not yet fully understand the biological mechanisms underlying its development and persistence. Most pain-relieving medications for chronic pain target nerve cells, yet it is becoming clear that non-nerve (non-conducting) cells also play an important role in

some chronic pain conditions. Matrix metalloproteases (MMPs) are enzymes that break down the medium surrounding tissue cells. MMPs also activate several pro-inflammatory proteins that stimulate the non-nerve conducting function of of the supportive glial cell. Scientists are wondering if neuropathic pain and inflammation are linked by a common mechanism involving MMP activation. Researchers found that a specific matrix metalloprotease, MMP9, showed increased activity soon after nerve injury, which stimulated the glial cells in the spinal cord, but this increased activity declined after several days. A different enzyme, MMP2, also was increased, but at later times after injury; this increase led to activation of another nerve-supportive cell in the spinal cord. The research showed that the pain response of nerve-injured animals were blocked early by inhibitors of MMP9 or later by inhibitors of MMP2. These findings suggest an important role for MMP9 in the onset of chronic neuropathic pain conditions, and for MMP2 in the persistence of those conditions. The results also demonstrate the complex interplay between nerve cells and several non-nerve cells. This research describes a novel set of molecules involved in neuropathic pain, and points scientists toward new targets for possible interventions to short-circuit the onset and persistence of chronic pain conditions.

→ Kawasaki Y, et al. *Nat Med* 2008;14(3):331-6. PMID: 18264108. PMCID: PMC2279180.
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDCR**)

Promising Approaches to Treating Chronic Pain: Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can result in addiction, tolerance, and physical dependence, all of which may undercut their value in some patients. Thus, an area of enormous need is the development of potent analgesics with diminished abuse liability for treating chronic pain. In response, NIH has implemented an aggressive and multidisciplinary research program that is yielding tangible results, which stand to revolutionize the field of pain management. At the molecular level, cannabinoid (CB) research has shown that it is possible to activate the CB system selectively to provide analgesia with minimal or no effects on mental function, and no abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different (heteromeric) receptors. Targeting them could provide a vastly expanded range of pharmacotherapeutics. This approach has already ushered in the development of promising designer molecules that can block pain more selectively and safely. At the cellular level, active research on non-neuronal brain cells has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their proinflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of other analgesic drugs. At the brain circuit level, a new approach has been developed to harness the brain's intrinsic capacity to train itself through a strategy in which subjects “learn” how to regulate pain by viewing, and then controlling, images of their own brains in real time.

→ Varga EV, et al. *Curr Mol Pharmacol* 2008;1(3):273-84. PMID: 20021440.
Ferre S, et al. *Trends Neurosci* 2007;30(9):440-6. PMID: 17692396.
Daniels DJ, et al. *Proc Natl Acad Sci U S A* 2005;102(52):19208-13. PMID: 16365317. PMCID: PMC1323165.
Ledeboer A, et al. *Expert Opin Investig Drugs* 2007;16(7):935-50. PMID: 17594181.
deCharms RC. *Trends Cogn Sci* 2007;11(11):473-81. PMID: 17988931.
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDA**, NINDS)

The Spine Patient Outcomes Research Trial (SPORT) for Low Back Pain: Before SPORT, many people who had chronic low back pain were conflicted about whether to undergo surgery; some were not sure surgery was worth the risk, while others feared that delaying surgery might cause even more damage. In the past 4 years, SPORT demonstrated that, indeed, surgery is superior to nonoperative treatments for the 3 most common causes of severe low back pain: intervertebral disk herniation and lumbar spinal stenosis with or without degenerative spondylolisthesis (the slipping of vertebrae). However, people who have one of these conditions are not subjecting themselves to further harm if they adopt a “wait-and-see” approach before committing to surgery. The benefits of surgery to correct spinal stenosis, for example,

were apparent as early as 6 weeks after surgery. Those patients who had severe slippage and discomfort due to lumbar spinal stenosis with degenerative spondylolisthesis seemed to benefit the most. Although people who did not have surgery reported some improvement 2 years into the study, those who had surgery seemed to be doing considerably better. Additionally, SPORT showed that combining two surgical procedures—decompressive laminectomy and fusion—did not help patients who had lumbar spinal stenosis without degenerative spondylolisthesis any more than decompressive laminectomy alone did. The findings regarding intervertebral disk herniation equally were meaningful. Two years after surgery, patients who had surgery for a herniated upper lumbar disk felt significantly better than those who had a lower disk repaired. Although more costly than nonoperative approaches, such as medications and physical therapy, lumbar diskectomy is a cost-effective treatment, regardless of whether the damaged disk is in the upper or lower portion of the lumbar spine.

→ Lurie JD, et al. *J Bone Joint Surg Am* 2008;90(9):1811-9. PMID: 18762639. PMCID: PMC2657310.
Tosteson AN, et al. *Ann Intern Med* 2008;149(12):845-53. PMID: 19075203. PMCID: PMC2658642.
Tosteson AN, et al. *Spine* 2008;33(19):2108-15. PMID: 18777603.
Weinstein JN, et al. *Spine* 2008;33(25):2789-800. PMID: 19018250. PMCID: PMC2756172.
Weinstein JN, et al. *N Engl J Med* 2007;356(22):2257-70. PMID: 17538085. PMCID: PMC2553804.
Weinstein JN, et al. *N Engl J Med* 2008;358(8):794-810. PMID: 18287602. PMCID: PMC2576513.
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAMS**, CDC/NIOSH, ORWH)

Acupuncture-Like Treatments Improve Outcomes Compared With Usual Care for Low-Back Pain: Chronic low-back pain is a common condition that can be difficult to treat. In a recent NIH-funded clinical trial, researchers at the Group Health Center for Health Studies in Seattle compared the efficacy of acupuncture, simulated acupuncture, and conventional care for chronic low-back pain. In the trial, 638 adults with chronic low-back pain were randomly assigned to 1 of 4 groups: individualized acupuncture, involving a diagnostician's customized prescription for needle placement; standardized acupuncture, using a single prescription for acupuncture points that experts consider generally effective for chronic low-back pain; simulated acupuncture, which mimics needle acupuncture without actual penetration of the skin; or usual care, which is standard medical care. At 8 weeks, all 3 acupuncture groups improved their dysfunction scores significantly more than the group receiving usual care. However, there was no significant difference between the groups receiving the actual and simulated acupuncture. Neither tailoring acupuncture needle sites to an individual patient nor penetrating the skin appears to be important for receiving therapeutic benefit. Although the researchers were encouraged that acupuncture-like treatments appear to be helpful for people suffering from low-back pain, the finding that actual acupuncture produced no greater benefit than simulated acupuncture raises important questions about acupuncture's mechanisms of action. The researchers recommend further research to determine the roles of patient expectancy, practitioner reassurance, and the physiological effects of noninsertive stimulation and other effects that may contribute to acupuncture-like benefits.

→ Cherkin DC, et al. *Arch Intern Med* 2009;169(9):858-66. PMID: 19433697.
→ For more information, see http://nccam.nih.gov/news/2009/051109.htm
→ (E) (**NCCAM**)

Neurobiology of Pain in Sickle Cell Disease: The past 35 years have produced a remarkable expansion in scientific understanding of the neurobiological basis of pain, yet none of this research has been specifically focused on sickle cell disease (SCD), one of the few human diseases associated with lifelong, often severe, pain. To address this gap, an NIH-sponsored working group brought together researchers studying the neuroscience of pain and hematologists having a special interest in SCD. Participants identified an urgent need for multidisciplinary studies encompassing neurobiology, hematology, pharmacology, and psychology. Based on the working group findings, in November 2008, NIH issued a request for grant applications, Exploratory Studies in the Neurobiology of Pain in Sickle Cell Disease, to support basic and translational studies on the distinctive aspects of pain syndromes in SCD.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-008.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NHLBI**, NINDS)

Developing Interventions to Improve Palliative Care at the End of Life: The life expectancy of the American people has reached a historic high, but along with increased life expectancy comes an increase in the number of people living with, and dying from, chronic debilitating diseases. Prolonged courses of decline at the end of life, palliative treatment options, and life-sustaining technologies have raised many important research questions within the last decade. In addition, the needs of dying children and their families are coming into greater focus, because death in childhood stands out as a particular tragedy and a unique end-of-life experience for all involved. To address these needs, NIH-supported end-of-life science seeks to understand dying with respect to the needs of dying persons and formal and informal caregivers. It includes research on issues such as: alleviation of symptoms, psychological care, near-death preferences, advance directives, and family decision-making. Likewise, end-of-life research addresses the cultural, spiritual, age-specific, and disease-specific factors that make each person's experience at the end of life unique. In FY 2009, NIH announced a funding initiative to develop and test interventions to enhance end-of-life and palliative care that providers can implement across multiple settings, illnesses, and cultural contexts. NIH made the first awards under this solicitation in late FY 2009.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-09-004.html
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NINR**, NCI)

Behavioral Strategies to Improve Quality of Life and Chronic Disease Outcomes: While health care advances continue to transform previously acute/fatal conditions into chronic conditions and individual life expectancy is increasing, issues of quality of life have become ever more important. Studies focusing on the management of disease- and treatment-related symptoms have demonstrated the capacity for behavioral strategies to mitigate effects of symptoms and contribute to improving short- and long-term patient outcomes. For example, behavioral strategies have been shown to improve patient outcomes across various diseases including diabetes, irritable bowel syndrome, and asthma. In recognition of the need for new behavioral strategies to manage chronic illness, NIH has established a goal of developing and testing behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes by 2012. Beginning in FY 2008, progress toward achieving this goal has been updated annually in the Online Performance Index section of NIH's portion of the President's budget submission to Congress.

→ For more information, see http://officeofbudget.od.nih.gov/br.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NINR**, NCI) (GPRA)

A Commitment to Global Health

A Nationally Representative Case-Control Study of Smoking and Death in India: Background: Recent evidence suggests that there are 120 million smokers in India. While smoking is registering a steady decline in western countries, experts estimate that it is increasing in India. Despite the magnitude of the smoking epidemic in India, there are no reliable studies that have assessed the effects of prolonged smoking of cigarettes or “bidis” on mortality. Advance: This is the first nationwide study conducted to assess the hazards of smoking among men and women in India. About 1.1 million homes in India were surveyed from 2001-2003. Researchers compared the smoking histories of 74,000 adults who had died during the study period against 78,000 unmatched controls. The study found that more than 30 percent of men and 5 percent of women aged 30-60 years smoked regular cigarettes or bidis. Smoking was associated with a 6- and 8-year reduction in median survival for men and women, respectively. The study confirmed that there are no safe levels of smoking.

Significance: The results of this landmark study were published in several Indian newspapers in February 2008, thereby informing the public and policy makers on the impact of smoking in India. In response to this study, the Indian Health Minister said that "The Government of India is trying to take all steps to control tobacco use—in particular by informing the poor and the illiterate." This science advance supported by NIH's International Tobacco and Health Research and Capacity Building Program provides important evidence on the smoking epidemic in India and lays the foundation on which tougher smoking standards can be enforced.

→ Jha P, et al. *N Engl J Med* 2008;358(11):1137-47. PMID: 18272886.
→ For more information, see http://www.hindu.com/2008/02/14/stories/2008021455551300.htm
→ For more information, see http://content.nejm.org/cgi/content/full/358/11/1137
→ For more information, see http://www.fic.nih.gov/programs/research_grants/tobacco/
→ (E) (**FIC**, NCI)

Global Health Initiative in Cardiovascular and Lung Diseases: In June 2009, NIH joined the United Health Chronic Disease Initiative and established a network of 11 Collaborating Centers of Excellence in low- and middle-income countries to build sustainable programs to combat chronic cardiovascular and lung diseases. The Centers are developing infrastructures for research and training to enhance their capacity to conduct population-based clinical research to monitor, prevent, or control chronic diseases. Each Center pairs a research institution in a developing country with at least one academic institution in a developed country. Nine of the 11 main developed country partners are institutions located in the United States. The program is expected to stimulate clinical, epidemiological, behavioral, and translational research, as well as research on health services, treatment outcomes, and health policy.

→ Nabel EG, et al. *Lancet* 2009;373(9680):2004-6. PMID: 19523681.
Daar AS, et al. *Nature* 2007;450(7169):494-6. PMID: 18033288.
→ For more information, see http://www.nhlbi.nih.gov/about/globalhealth/index.htm
→ (E) (**NHLBI**)

2009 Institute of Medicine Report, The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors: The recently released IOM report, *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*, reviews U.S. interest and investment in global health. This new report is particularly timely and useful given the major changes in global health that have occurred since the last IOM report, *America's Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests*, was released in 1997. These changes include unprecedented interest and large fiscal commitments to global health by the U.S. government and nongovernmental sectors. The IOM leveraged the contributions of 18 NIH ICs to undertake this update with additional financial support from several key private and public entities. The study makes the case for why U.S. agencies and private sector entities should invest more heavily in global health. The report has five key recommendations that can inform NIH investments in global health in the coming years:

- Scale up existing interventions to achieve significant health gains
- Generate and share knowledge to address health problems endemic to the global poor
- Invest in people, institutions, and capacity building with global partners
- Increase U.S. financial commitments to global health
- Set the example of engaging in respectful partnerships

The IOM panel was chaired by Dr. Harold Varmus and Ambassador Thomas Pickering. A preliminary report, titled *The U.S. Commitment to Global Health: Recommendations for the New Administration*, was released in December 2008. In May 2009, the final report, titled *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*, was released.

→ For more information, see http://www.iom.edu/Reports/2009/The-US-Commitment-to-Global-Health-Recommendations-for-the-Public-and-Private-Sectors.aspx
→ For more information, see http://www.iom.edu/Reports/2008/The-US-Commitment-to-Global-Health-Recommendations-for-the-New-Administration.aspx
→ This example also appears in Chapter 2: Cancer, Chapter 2: Infectious Diseases and Biodefense and Chapter 3: Clinical and Translational Research
→ (O) (**FIC**, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS)

Millennium Promise Awards: World Health Organization (WHO) statistics show that about 60 percent of all deaths worldwide are attributable to chronic diseases, and 80 percent of them occur in low- and middle-income countries (LMICs). To address the significant and growing burden of chronic disease in LMICs, in July 2008, NIH launched a $1.5 million-a-year grant program, Millennium Promise Awards: Noncommunicable Chronic Diseases Research Training Program to support the training of researchers to fight chronic diseases in LMICs. This research training program is designed to build research capacity in LMICs in fields related to cancer; cerebrovascular disease including stroke; lung disease including chronic obstructive pulmonary disease and environmental factors including indoor air pollution; obesity and lifestyle factors related to these conditions; and genetics of noncommunicable diseases. The objectives of the program are to train a cadre of experts in LMICs who can assess the magnitude of chronic diseases in LMICs; address chronic diseases in a culturally relevant and sensitive manner; develop methods to monitor and understand the causes of chronic disease; work in chronic diseases across a broad range of research areas from genetics to implementation science; and translate research into public health policy and programs.

→ For more information, see http://www.fic.nih.gov/programs/training_grants/ncod/index.htm
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-175.html
→ (E) (**FIC**, NCI, NICHD, NIEHS, NINDS, NINR, ODP/ODS)

NIH Strategic Plans Pertaining to Chronic Diseases and Organ Systems

National Heart Lung and Blood Institute (NHLBI)

- *NHLBI Strategic Plan: Shaping the Future of Research*

National Cancer Institute (NCI)

- *NCI Strategic Plan for Leading the Nation*

National Institute of Dental and Craniofacial Research (NIDCR)

- *NIDCR Strategic Plan*
- *NIDCR Implementation Plan*

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Strategic Plans:

- *National Diabetes Education Program (NDEP) Strategic Plan*
- *Overcoming Bladder Disease—A Strategic Plan for Research*
- *Renal Disease Research Plan*
- *Strategic Plan for Polycystic Kidney Disease*

- *Strategic Plan of the National Kidney Disease Education Program (NKDEP)*
- *Strategic Plan for Pediatric Urology: The Strategic Plan for Pediatric Urology, NIDDK—Research Progress Report*
- *NIDDK Prostate Research Strategic Plan*

Reports from Planning Activities:

- *Clinical Research on Kidney Disease*
- *NIDDK Annual Compendium of Recent Advances and Emerging Opportunities*
- *Progress Report on NIDDK Efforts to Promote Translational Research*
- *Research Needs in Pediatric Kidney Disease—2000 and Beyond*
- *Strategic Planning for Polycystic Kidney Disease*
- *Urolithiasis Research Symposium*

National Institute of Allergy and Infectious Diseases (NIAID)

- NIH Autoimmune Diseases Coordinating Committee: *Progress in Autoimmune Diseases Research (2005)*
- *Report of the Expert Panel on Food Allergy Research (2006)*
- *NIH Action Plan for Transplantation Research (2007)*

National Eye Institute (NEI)

- National Eye Institute Strategic Planning
- *National Plan for Eye and Vision Research (2004)*
- *Progress in Eye and Vision Research 1999-2006*
- Ocular Epidemiology Strategic Planning Panel Report—Epidemiological Research: From Populations Through Interventions to Translation (2007)
- *Age-Related Macular Degeneration Phenotype Consensus Meeting Report*
- *Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration Workshop Report*
- *Report of the Advances in Optical Imaging Symposium*

National Institute on Aging (NIA)

- *Living Long and Well in the 21st Century: Strategic Directions for Research on Aging*

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

- *NIAMS Long-Range Plan: Fiscal Years 2006-2009*
- *NIAMS Long-Range Plan: Fiscal Years 2010-2014*

National Institute of Mental Health (NIMH)

- *The National Institute of Mental Health Strategic Plan*

National Institute on Drug Abuse (NIDA)

- *NIDA Five-Year Strategic Plan 2009*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- *National Institute on Alcohol Abuse and Alcoholism Five Year Strategic Plan FY08-13*

  Recommendations of the NIAAA Extramural Advisory Board (EAB):

  - *Developing an NIAAA Plan for HIV-Related Biomedical Research*
  - *Fetal Alcohol Spectrum Disorders Research*
  - *Mechanisms of Alcohol Addiction*
  - *Mechanisms of Behavioral Change*
  - *Gut-Liver-Brain Interactions in Alcohol-Induced Pathogenesis*
  - *Mechanisms of Alcohol Action and Injury*
  - *Medications Development*

National Institute of Nursing Research (NINR)

- *NINR Strategic Plan: Changing Practice, Changing Lives*

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

- *Contraception and Reproductive Health Branch (CRHB), NICHD, Report to the NACHHD Council, June 2008*
- *Endocrinology, Nutrition, and Growth (ENG) Branch Report to Council*

National Center for Complementary and Alternative Medicine (NCCAM)

- *Expanding Horizons of Health Care: Strategic Plan 2005-2009*

John E. Fogarty International Center (FIC)

- Pathways to Global Health Research: Strategic Plan 2008-2012

Office of AIDS Research (OAR)

- *FY 2008 Trans-NIH Plan for HIV-Related Research*
- *FY 2009 Trans-NIH Plan for HIV-Related Research*
- *FY 2010 Trans-NIH Plan for HIV-Related Research*

Office of Dietary Supplements (ODS)

- *Promoting Quality Science in Dietary Supplement Research, Education, and Communication: A Strategic Plan for the Office of Dietary Supplements, 2004-2009*

Trans-NIH Strategic Plans

- *Strategic Plan for NIH Obesity Research*
  (CSR, DNRC, FIC, NCCAM, NCI, NCMHD, NCRR, NHGRI, **NHLBI**, NIA, NIAAA, NIAMS, NIBIB, NICHD, NIDA, NIDCR, **NIDDK**, NIEHS, NIMH, NINDS, NINR, OBSSR, ODP, ODS, ORWH, OSP)

- *Action Plan for Liver Disease Research*
  (CSR, FIC, NCCAM, NCI, NCRR, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCR, **NIDDK**, NIEHS, NIGMS, NINDS, NINR, NLM)
- *NIH Action Plan for Transplantation Research (2007)*
  (NCI, NHLBI, NIA, NIAAA, **NIAID**, NIAMS, NIBIB, NIDA, NIDCR, NIDDK, NIMH, NINDS)
- Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases
  (NINR, ORWH, NIA, NICHD, **NIDDK**, NIBIB, NIDA, NCCAM, NIEHS, NCI, NIGMS, NIAID, NCMHD, NIAAA)

Detailed Burden of Illness and Related Health Statistics

Although a comprehensive listing of burden estimates for all chronic diseases is not feasible within the format of this document, the following summary illustrates the depth and breadth of the chronic disease burden:

Cardiovascular Diseases[113]

Coronary heart disease
Mortality: 446,000 (2005)
Prevalence: 16.8 million (2006)

Heart failure
Mortality: 57,000 (2004)
Prevalence: 5.7 million (2006)

Arrhythmias
Prevalence: > 2 million with atrial fibrillation

Congenital heart defects
Incidence: 8 of every 1,000 newborns (35,000 per year)
Prevalence: 1 million adults

Peripheral arterial disease
Prevalence: 8-12 million

Lung Diseases[114]

Chronic obstructive pulmonary disease
Mortality: 127,000 (2005)
Prevalence: 12 million people diagnosed; additional 12 million undiagnosed (2006)

Asthma
Mortality: 4,000 (2005)
Prevalence: 23 million (2006)
Total costs (direct and indirect): $19.7 billion (2007)

Cystic Fibrosis
Prevalence: 30,000
Incidence: 1,000 new cases per year

Diabetes Mellitus[115]

Mortality: 233,619 (2005); 7th leading cause of death
Prevalence: 23.6 million (diagnosed and undiagnosed); type 1 diabetes accounts for 5-10% of diagnosed cases (2007)
Total costs (direct and indirect): $174 billion (2007)

Obesity[116]	Prevalence: 34.6% of adults are overweight; 31.4% of adults are obese; 17.1% of children (aged 6-11) and 17% of adolescents (aged 12-19) are overweight (2006) Total health care costs (direct and indirect): $117 billion (2002)
Chronic Kidney Disease[117]	Prevalence: 11.5% of adults age 20 or older (23.2 million people) (1999-2000) Costs: $33.6 billion in public and private spending for treating end-stage renal disease (ESRD) (2006)
Urologic Diseases[118]	***Benign prostatic hyperplasia*** Prevalence: 6.5 million Caucasian men aged 50-79 (2000) Cost (direct): $1.1 billion (2000) ***Painful bladder syndrome/interstitial cystitis*** Prevalence: 0.8% of women (1.2 million) and 0.1% of men (0.08 million) (1988-1994) Cost (direct): $65.9 million (2000) ***Kidney stones*** Prevalence: 5% of adults (1988-1994) Cost: $2.07 billion (2000) ***Urinary incontinence*** Prevalence: 38% of women and 17% of men, aged 60 and older (1999-2000) Cost (direct): $463.1 million ***Urinary tract infection*** Prevalence: 13% of women (12.8 million) and 2.3% of men (2 million) had a UTI in the last 12 months (1994) Cost (direct): $3.5 billion (2000)
Digestive Diseases[119]	Mortality: 236,000 (2004) Prevalence: 60-70 million people (1996) Disability: 1.9 million people unable to perform daily activities (1990-1992) Costs: $97.8 billion (direct); $44 billion (indirect) (2004)
Chronic Liver Disease[120]	***Chronic liver disease or cirrhosis*** Mortality: 27,013; 12th leading cause of death (2004) Prevalence: 5.5 million people (2-3% of adults) (1998) Cost (direct and indirect): $1.6 billion (1998) ***Gallbladder disease*** Mortality: 3,086 (2004) Prevalence: 12% of adults (20 million) (1998) Cost: $6.4 billion (2004) ***Viral hepatitis*** Mortality: 5,000 (Hepatitis B); 8,000-10,000 (Hepatitis C) Prevalence: 1.25 million (Hepatitis B); 3.2 million (Hepatitis C) with chronic infection (1999-2002) ***Alcoholic liver diseases*** Mortality: 12,201 (2001) Years of potential life lost (YPLL): 316,321 (2001)

Blood Diseases[121]

Sickle cell disease
Prevalence: 70,000; 1 in 500 African American births
Thalassemia (includes Cooley's anemia)
Prevalence: 1,000
Hemophilia
Prevalence: 18,000
Incidence: 400 newborns each year

Musculoskeletal Diseases[122]

Osteoarthritis
Prevalence: 12.1% of adults (27 million)
Osteoporosis
Prevalence; 10 million adults, 80% of whom are women; 34 million have low bone mass
Disability: > 1.5 million fractures
Costs (direct): $14 billion
Osteogenesis Imperfecta
Prevalence: 20,000-50,000
Paget's disease of bone
Prevalence: 1 million

Skin Diseases and Conditions[123]

Prevalence: At any given time, 1 in 3 people has a skin condition.
Total health care costs: > $29.1 billion (2004)
Atopic dermatitis
Prevalence: 10-20% of children and 1-3% of adults are affected
Total health care costs: > $3 billion

Eye Diseases[124]

Age-related macular degeneration
Prevalence: 1.75 million; leading cause of vision loss in persons age 65 or older (2004)
Uveitis
Prevalence: 115.3 cases per 100,000 persons (2004)
Disability: 30,000 new cases of blindness (1990)
Diabetic retinopathy
Prevalence: 4.1 million adults aged 40 or older (2004)
Glaucoma
Prevalence: 2.2 million

Deafness[125]

Hearing loss
Prevalence: 2-3 of 1,000 newborns; 17% (36 million) adults; 15% (26 million) adults aged 20-69 suffer hearing damage due to noise exposure
Otitis media (middle ear infection)
Cost: $5 billion
Balance and dizziness
Prevalence (balance): 4% (8 million)
Prevalence (dizziness): 1.1% (2.4 million)
Cost: $8 billion for falls by older adults

Dental and Craniofacial Disorders[126]	***TMJ disorder*** Prevalence: 5-12% of the population; twice as prevalent in women as men Cost: $4 billion ***Chronic periodontitis*** Prevalence: 80% of adults with 1 in 5 having severe periodontitis
Mental Disorders[127]	***Mental disorders*** Prevalence: 6% of adults (approximately 12.5 million) have a serious mental disorder Disability: No. 1 leading cause; accounts for 24% of all disability adjusted life years (DALYs) (U.S. and Canada, ages 15-44) Cost: $198 billion annually in lost earnings; total direct and indirect annual costs of mental illness are more than $300 billion ***Depression*** Prevalence: Major depressive disorder affects approximately 6.7% of American adults (approximately 14.8 million people) Disability: leading cause among mental health disorders; accounts for 7.5% of all DALYs (North and South America) Cost: $36.2 billion due to lost work; $51.5 billion including lost productivity while at work
Alcohol Use Disorders[128]	***Alcohol use disorders*** Prevalence: 19.3 million (7.8% of the population aged 12 or older) ***Alcohol-attributable chronic disease*** Total costs: $155 billion (est.) Disability: Alcohol use is the 7th leading cause of DALYs
Addiction[129]	Total cost: > $600 billion (est.; includes health- and crime-related costs as well as losses in productivity)—approximately $181 billion for illicit drugs, $193 billion for tobacco, and $235 billion for alcohol. ***Abuse or dependence on alcohol and illicit drugs*** Prevalence: 22.2 million people or 9% of the population aged 12 or older (SAMHSA/NSDUH 2008) ***Cigarette smoking*** Mortality: 443,000 (CDC Fast Facts Sheet)
Pain[130]	76.2 million, or 1 in every 4 Americans, have suffered from pain that lasts longer than 24 hours in the past month and millions more suffer from acute pain. One in 10 persons with pain reports it lasting for a year or more.

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[107] For more information, see National Health Interview Survey, 2006, public use data file. Available at: http://www.cdc.gov/nchs/nhis.htm.
[108] The screening tool and associated resources are available at http://www.nida.nih.gov/nidamed/.
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Life Stages, Human Development, and Rehabilitation

The development of a vaccine for Haemophilus influenza type *b (Hib) is one of NIH's important contributions to public health. Work on this vaccine began several decades ago when NIH intramural researchers Drs. John B. Robbins and Rachel Schneerson were investigating ways to protect infants and young children from Hib. At the time, this often-fatal bacterial infection was the leading cause of meningitis (inflammation of the brain) among children under the age of 5 in the United States. Even with effective antibiotic treatment, 5 percent of the 20,000 children who contracted Hib each year died; about 30 percent were left with intellectual and developmental disability (IDD), deafness, or seizures. Hib meningitis was the leading cause of acquired IDD in the Nation at that time. With the help of research colleagues Drs. David Hamilton Smith and Porter Warren Anderson, Robbins and Schneerson developed a vaccine that proved effective in combating Hib. And, unlike previous attempts at a Hib vaccine, the Robbins-Schneerson version was effective in infants, the population that needed the most protection. Since the vaccine was licensed in 1987, Hib cases have been disappearing rapidly. Today, fewer than 100 cases of invasive Hib infection, almost none with meningitis, occur in the United States each year. This research has virtually eliminated the leading cause of acquired IDD in the United States. With widespread use of the vaccine, it may be possible to end this disease throughout the world.*

Introduction

Interactions among biological processes and physical and psychosocial factors in the environment shape an individual's health and functional capacities from the earliest formation of cells, tissues, organs, and organ systems through childhood, adulthood, and old age. NIH research focuses on healthy developmental processes and the ways in which these processes go off track, causing or contributing to much of the Nation's heavy burden of disease and disability. Some disorders of altered developmental processes, such as neural tube defects, are apparent at birth. Others, including intellectual and developmental disabilities, obesity, cardiovascular and metabolic diseases, cancers, mental illnesses, and dementias, may not emerge until months, years, or decades later.

Human development progresses most rapidly during gestation and early childhood but continues throughout the course of life. Each developmental stage lays the foundation for health or illness in subsequent stages. This means that the developmental aspects of NIH research have critical implications for public health. Understanding precisely what happens during developmental "windows" of heightened sensitivity to infections, toxic exposures, personal behaviors, and a host of other environmental factors is essential to learning how and when to intervene most effectively to prevent or lessen chronic and disabling conditions. For example, NIH-supported researchers recently showed that early intervention for 2-year-olds with speech delay can help most of them catch up with their more talkative peers by age 7.[131] In another example, NIH-supported research indicates that older people can delay some losses of function associated with the normal aging process with moderate exercise, satisfactory nutrition, and certain other personal behaviors.[132]

NIH-supported researchers recently showed that early intervention for 2-year-olds with speech delay can help most of them catch up with their more talkative peers by age 7.

This area of NIH research also encompasses medical rehabilitation, including tissue regeneration, to optimize the functioning of individuals with disabling conditions. Medical rehabilitation research is the study of physiologic mechanisms, methods of treatment, and devices that serve to improve, restore, or replace underdeveloped, lost, damaged, or deteriorated function. A key aspect of medical rehabilitation research is its focus on the effects of functional problems on the whole person, rather than a single organ system. Thus, it views the individual in the context of a dynamic system of interacting variables, including organic, psychosocial, and environmental factors.

The role of developmental processes in the risks for common and rare disorders and in rehabilitation science means that the scope of NIH research in life stages, human development, and rehabilitation is quite broad. This research area includes basic research on molecular and cellular processes to gain insights into the trajectories of human development and disease and even to harness developmental processes such as cell differentiation for therapeutic and rehabilitative uses. This research area also includes the collection and analysis of data over the lifespan or over a specific period of interest, such as childhood or aging. Such studies can suggest the relative contributions, to health or to specific disorders, of environmental exposures and ongoing developmental and disease processes. Also included are studies of specific disorders with an emphasis on an individual's life stage or developmental status.

As the Institute with statutory responsibility for child health and human development research, NICHD conducts and supports research programs in reproductive health and in the developmental processes that begin before conception and continue through adolescence. As the Institute with statutory responsibility for research on aging, NIA conducts and supports research on both the maintenance and loss of functions during the aging processes, diseases associated with aging, and the problems and needs of older individuals and their caregivers. NINR supports research across all life stages to build the scientific foundation for clinical practice and managing and eliminating symptoms caused by illness, and it also is the designated lead NIH Institute for end-of-life research. NIEHS focuses on the influences of environmental agents on the development and progression of specific diseases.

Numerous other ICs support life stages, human development, and rehabilitation research in cancer, diabetes, musculoskeletal and neurological disorders, and other areas relevant to their missions. ORWH, among its many roles, works across all ICs to develop opportunities for and support research and training opportunities for studying disorders relevant to women's health across the lifespan and sex and gender differences in disease. Mission-specific rehabilitation research is supported by multiple Institutes, including NIA, NIBIB, NICHD, NIDCD, NIDCR, and NINDS. A focal point for this research is NICHD's National Center on Medical Rehabilitation Research, which emphasizes the rehabilitation and lifelong care of people with physical disabilities resulting from stroke, injury, and other disorders.

Burden of Illness and Related Health Statistics

Many sections of this report include data on the burden of illness of specific conditions in which developmental-environmental interactions are or may be implicated. Comprehensive data on the total burden of these conditions do not appear to be available. The magnitude of this burden, however, is suggested by the complex problem of obesity and its associated conditions, including type 2 diabetes, cardiovascular disease, pregnancy complications, certain cancers, osteoarthritis, liver and gall bladder disease, and depression. The Centers for Disease Control and Prevention estimates the prevalence of obesity among individuals ages 20 years and older in the United States as 31.4 percent and the prevalence of obesity plus overweight as 66 percent. Overweight and obesity also exert a substantial economic toll on the United States, with the combination of direct health care costs plus indirect costs, such as lost wages caused by illness, estimated to be $117 billion for the year 2002.[133]

Although the mechanisms are not well understood, the developmental dimensions of obesity are evident in several types of data that implicate, for example, the uterine environment in birth defects and other significant problems. Maternal obesity during pregnancy appears to independently interfere with embryonic development, leading to increased risks of congenital abnormalities, particularly neural tube defects (NTDs). Conventional folic acid supplementation during pregnancies of obese women appears to be ineffective in preventing NTDs.[134] Children of mothers who were obese during pregnancy are at significantly higher risk of developing the metabolic syndrome, a combination of conditions that include obesity and cardiovascular and metabolic disorders, notably type 2 diabetes, in childhood.[135] Children of mothers with type 2 diabetes during pregnancy, a condition associated with obesity, are at elevated risk for a range of neurodevelopmental problems that affect childhood motor functioning, attention span, activity level, and learning ability. To some investigators, these symptoms suggest a possible association with later-emerging schizophrenia.[136]

Obesity and its associated medical conditions so compromise quality of life and escalate medical costs that finding effective interventions, especially for early stages of life, is a major health priority. A recent estimate placed the costs of inpatient care alone of children with an obesity diagnosis (primary or secondary) at $237.6 million in 2005.[137] At the other end of the age spectrum, approximately 80 percent of individuals in the United States ages 65 years or older have at least 1 chronic condition and 50 percent have at least 2. Almost half of lifetime expenditures, 48.6 percent, are attributed to the 65-and-older population in the United States.[138]

Estimating the burden of functional limitations for which rehabilitation may be indicated is complicated by lack of consensus on the definition of "disability," appropriate survey measures, and other issues. The Institute of Medicine (IOM) defines disability as impairments in body structure or function, limitations on activities such as dressing and other daily personal care, and limitations on participation in such activities as school and work. IOM reported that between 40 million and 50 million individuals, or about 1 in 7 Americans, have some type of disability.[139]

NIH Funding for Life Stages, Human Development, and Rehabilitation Research

Actual NIH funding support levels for rehabilitation research were $403 million in FY 2008, and $404 million and $75 million in FY 2009, respectively, for non-ARRA (regular appropriations) and ARRA (Recovery Act appropriations). Currently, NIH does not collect the trans-NIH funding data necessary to provide an aggregate figure for expenditures on life stages, human development, and rehabilitation. Click on the funding levels, which are live links, to produce detailed project listings. These lists are derived from the NIH Research, Condition, and Disease Categorization (RCDC) system. In addition, the table at the end of this chapter indicates some of the research areas involved in this investment (see *Estimates of Funding for Various Research, Condition, and Disease Categories*).

Summary of NIH Activities

The goal of NIH life stages, human development, and rehabilitation research is to enable individuals to achieve a full lifespan with the best health and function at every life stage. Understanding complex developmental pathways to health or illness throughout the life course is critical to creating new ways to prevent disease and disability before they become symptomatic, or even preempting the disease process before it starts. Basic, clinical, and translational research all rest on the fundamental concept of developmental science, that the formation and function of cells, tissues, organs, organ systems, and the fully formed individual are sensitive to protective or harmful environmental factors, and especially so at specific stages. These factors include physical agents, such as industrial and agricultural chemicals, tobacco and alcohol, microbial infections, nutritional deficits, and even medical treatments such as pharmaceuticals and radiation. Powerful environmental influences also include behaviors of individuals and of the people with whom a person lives or works, and norms and values of households, families, schools, workplaces, and communities. Sex and gender differences affect developmental trajectories and disease risks. All such factors can have immediate, intermediate, and/or long-term effects on human health and function.

Human Development

In studies of the most fundamental molecular and cellular processes, NIH scientists continually expand understanding of how development typically progresses, what goes awry and why, and how health is affected (also see the section on *Molecular Biology and Basic Sciences* in Chapter 3). For example, "epigenetic" influences on the expression of genes may be critical mechanisms for gene/environment interactions that influence health and development. Understanding these subtle interactions is an essential step toward discovering treatments and preventive strategies. Scientists recently investigated a type of epigenetic modification, known as DNA methylation, by exposing pregnant yellow agouti mice to bisphenol A, an organic compound found in plastics and plastic additives whose safety has been questioned. The scientists found that maternal exposure to the compound altered the coat color in the offspring by decreasing the methylation at a

critical point. Moreover, they found that they could reduce this effect by simply supplementing maternal diets with either folic acid or an estrogen-like chemical found in plants.[140]

NIH has established the Roadmap Epigenomics Program to stimulate the creation of important new scientific resources for epigenetics researchers and thus speed progress toward applications that affect human health and common, complex human diseases. A major effort in the program is characterizing the epigenome, that is, creating a catalog of stable epigenetic modifications that occur in the genome (all genes encoded in the DNA). Among other things, Roadmap epigenomics resources may become the basis for studies of diabetes, including the effects of the intrauterine environment on later risk of this disorder.

Basic research in developmental biology also may enable scientists to harness powerful normal processes in the lives of cells for therapeutic purposes.

Basic research in developmental biology also may enable scientists to harness powerful normal processes in the lives of cells for therapeutic purposes. Research on cell senescence, a prominent mechanism of normal aging, one day may yield understanding of cellular mechanisms that act to block the development of cancer as well as specific characteristics of aging. Goals of human embryonic stem cell research include explaining critical events in early human development that could lead to developing customized regenerative medical interventions. Sex and gender differences affect developmental trajectories and disease risks. Basic research is only one essential component of the NIH portfolio of multiple methodological approaches to understanding human development. For example, with NIH support, investigators are assembling a unique database of anatomical neuroimages of children's developing brains over time. This database also will include clinical, behavioral, demographic, and cognitive data on the children, thus enabling scientists to understand the multiple dimensions of normal human brain development. Such understanding is essential to elucidating intellectual and developmental disabilities, pediatric neurological diseases, and many other disorders that emerge in childhood. The multidecade Baltimore Longitudinal Study of Aging (BLSA) has created a wealth of information that has helped scientists—and the public—understand distinctions between physical changes attributable to the aging process and those caused by disease.[141] These data have yielded important insights on, among other things, relationships between age-related changes in the arteries and cardiovascular disease and differences between normal declines in cognitive ability related to age and those associated with Alzheimer's disease (AD) and related conditions.

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Life Stages

"Life stages" or "life course" research is a concept that informed landmark epidemiological and longitudinal studies. These studies linked risks of major adult-onset disorders, including diabetes, hypertension, stroke, and heart disease, to environmental influences in utero and in early childhood.[142] NIH research examples in this section illustrate how the life-course research model has expanded to include a greater number of developmental stages and a wide array of environmental factors and conditions of interest, with a goal of determining how—and when—to intervene to prevent or treat disease. NIH-supported investigators at Breast Cancer and Environment Research Centers are studying mammary gland development in animals and young girls to determine vulnerability to environmental agents that may explain emergence of breast cancer in adulthood. Among other projects, researchers are following a population of young girls to see how diet affects adipose (body fat) tissue and may alter hormonal control of sexual maturation. Although the data are mixed, there is some evidence of possible associations among childhood overweight and obesity, early onset of puberty and, in girls, later risk of breast cancer.[143,144]

NIH-supported research on maternal and childhood obesity seeks to understand complex interactions among genetic, psychological, physiological, familial, community, and other factors in this major public health problem. The goals of such research include understanding rapid, recent increases in rates of obesity and determining how and when to intervene to achieve lasting effect. NIH findings of high rates of overweight and other major risk factors for type 2 diabetes in middle school students are the basis for current trials of school-based diet and exercise interventions. The goal of the interventions is to decrease the children's short- and longer-term risks for obesity and diabetes. An ongoing study of the potential of substantially reducing caloric intake to prolong human life—as has been demonstrated in animals—has enhanced understanding of exercise as an important component to sustain weight loss. The Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) found that energy metabolism slows in response to caloric restriction, but that this "metabolic adaptation," which may make weight control more difficult, can be forestalled when exercise is added to dietary restriction.

NIH findings of high rates of overweight and other major risk factors for type 2 diabetes in middle school students are the basis for current trials of school-based diet and exercise interventions.

The tendencies toward risky behaviors attributed to immaturity of the brain in adolescence makes this developmental stage of interest in studies of substance dependency and addiction. In seeking to understand how developmental stage may influence vulnerability to, or protection from drug abuse, scientists are beginning to understand how a range of environmental variables, including quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics, influence brain development and behavior. Researchers also are testing preventive strategies such as physical activity and interactive Web-based technologies to engage young people. The NIH Underage Drinking Initiative similarly seeks to understand environmental, biobehavioral, and genetic factors that may influence progression in young people to harmful alcohol use, within the context of overall development. (Also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2.)

Better understanding of relationships between developmental stages and disease processes may be critical to the efficacy of therapeutic interventions. NIH scientists discovered that the retinal cells of children with the rare eye disorder, Leber congenital amaurosis (LCA), remain viable for several years, providing a window of opportunity to intervene. An early clinical trial already has shown that a gene transfer treatment for affected children is safe and improves visual function.[145] In another example, NIH-supported research on brain development in children with attention-deficit/hyperactivity disorder (ADHD) showed a normal pattern of brain development, but with a significant delay in maturation of the prefrontal cortex between the ages of 5 and 15 years. Scientists now are investigating the effects of treatment on rates of cortical maturation.

Research that led to universal newborn screening for phenylketonuria and for hypothyroidism and immediate initiation of treatment for affected infants to protect their developing brains has virtually eliminated intellectual and developmental disabilities (IDDs) associated with these conditions. NIH now is funding a major initiative to speed the development of highly efficient technology for screening newborns for very large numbers of additional rare genetic conditions and to accelerate the discovery of treatments for such conditions. This initiative also includes support for networked facilities to translate scientific discoveries quickly into clinical practice.

Other NIH investments in understanding and developing interventions for Fragile X and Down syndromes and other IDDs include support for 14 IDD centers. These centers provide core research resources in genetics and proteomics as well as clinical infrastructure for a wide range of studies. Multiple NIH-supported programs focus on autism and autism spectrum disorders (ASDs). For example, American Recovery and Reinvestment Act funding is being used to accelerate research in such areas as immune and central nervous system interactions that may help to explain the heterogeneity of ASDs. The Early Autism Risk Longitudinal Investigation (EARLI) is following a large cohort of mothers of children diagnosed with autism who are pregnant or planning another pregnancy. Among planned EARLI analyses are determining whether in

utero exposure to certain organic pollutants is associated with autism risk.[146] (Also see the sections on *Neuroscience and Disorders of the Nervous System* in Chapter 2 and *Autism Centers of Excellence* in Chapter 4.)

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Included in NIH research on conditions associated with adult life stages are studies to find and test safe and effective interventions for female pelvic floor disorders and for menopausal symptoms, both of which typically emerge in middle age. A comprehensive Longitudinal Mental Health Tracking System, now under construction, will bring together a wealth of epidemiological information that already is being collected. The new system will enable scientists to track the trajectories of mental disorders as well as their prevalence, incidence, severity, and other data over time.

Research on normal maturational processes may lead to new ways to treat or prevent disorders associated with aging. For example, genetics are known to play a role in the age-related hearing loss (presbycusis) that affects most individuals after age 60. A research team studying gene activity in the inner ear of a mouse model of presbycusis has identified multiple genes that are involved in programmed cell death (apoptosis), and determined that the activity of these genes increased as the mice aged and hearing loss progressed. This research raises the possibility that a drug may one day be developed that could stop or delay apoptosis of sound-detecting cells as they age in the human ear.[147]

In other research, NIH is supporting a clinical comparison of the safety and efficacy of two drugs for treating advanced age-related macular degeneration, a leading cause of vision loss in older individuals. A recent NIH review and analysis of its research program on geriatric translational neuroscience included a workshop to identify priority questions relating to causes of mental disorders in older individuals. Studies of age-related cognitive decline, distinct from Alzheimer's disease (AD) and other dementias, have yielded a wealth of data on positive effects of cognitive training, physical exercise, social engagement, stress reduction, and other strategies. The potential of this accumulated evidence prompted NIH to partner with foundations in supporting work to translate findings on cognitive aging into developing interventions that can be tested in clinical trials.

NIH is supporting a clinical comparison of the safety and efficacy of two approved drugs for treating advanced age-related macular degeneration, a leading cause of vision loss in older individuals.

NIH makes major investments in research to understand onset and progress of AD, the most common form of dementia in aging, and to discover how to slow its progress and, ultimately, to prevent it. An innovative public-private partnership, The Alzheimer’s Disease Neuroimaging Initiative (ADNI), has stimulated the development of more sensitive tools for tracking the development and progression of mild cognitive impairment and AD. Other ADNI projects include a genome-wide association dataset of study participants and a longitudinal study of cerebrospinal fluid samples collected from study participants.[148] Another major NIH investment in this area is in AD translational research, including drug discovery, preclinical development, and toxicology services for testing promising therapeutic compounds. Much of NIH’s clinical AD research is carried out through the Alzheimer’s Disease Cooperative Study (ADCS), conducted by a consortium of centers that are testing how to predict AD development in vulnerable individuals and develop ways to block its emergence or lessen its effects. ADCS projects include multiple trials of agents that may slow cognitive decline associated with AD, delay the emergence of AD-associated agitation and psychosis, and otherwise treat this devastating disorder.[149] (Also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2.)

At all stages of life, individuals with chronic or critical illnesses and their families and clinical caretakers need evidence-based guidance and support in managing chronic illness and transitioning to the end of life. End-of-life science seeks to understand dying with respect to the needs of dying persons and formal and informal caregivers. It includes research on

such issues as: alleviation of symptoms, psychological care, near-death preferences, advance directives, and family decision-making. Likewise, end-of-life research addresses the cultural, spiritual, age-, and disease-specific factors that make each person's experience at the end of life unique. NIH end-of-life research applies biological, behavioral, and social science strategies to advance the understanding of the dynamic interactions of these various factors and to develop interventions that optimize patient and caregiver quality of life across care settings and cultural contexts. NIH recently sponsored an initiative to develop and test interventions to enhance end-of-life and palliative care, which providers can implement across multiple settings, illnesses, and cultural contexts. NIH-supported Centers in Self Management or End-of-Life research are important loci for interdisciplinary research in this area. [150]

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Rehabilitation

The goal of rehabilitation science is to enable individuals with functional impairments associated with congenital disorders, chronic diseases, or events such as stroke or traumatic injury to live full and productive lives, as independently as possible. Developmental stages are a central consideration in this research because differences among age groups, including physiology and physical size, psychosocial trajectories, and expected lifespan, must all be taken into account in rehabilitation interventions.

Goals of research on neural prosthetic devices include improving cochlear implants for people with impaired hearing, and even enabling individuals with paralysis to directly control devices with their brains.

An important focus of rehabilitation research is the interface between medicine and engineering. Scientists explore innovative biomedical technologies and test their capacity to resolve stubborn medical problems and enhance mobility, sensory, and other functions of individuals with disabling conditions. Among current projects are efforts to develop advanced methods to eliminate infection when lower limb prostheses are attached directly to bones. Early findings on movement control are the basis for a new nerve-muscle graft procedure that significantly improves amputee control of a prosthetic device.[151] Goals of research on neural prosthetic devices include improving cochlear implants for people with impaired hearing, and even enabling individuals with paralysis to directly control devices with their brains.[152] NIH also supports development of sophisticated sensors for prosthetic devices and virtual reality systems to enhance rehabilitation.

Basic processes of cellular and molecular development and function offer great potential for rehabilitation research and clinical applications. Scientists are seeking to understand both the mechanisms that underlie functional impairments and the therapeutic potential of such basic developmental processes as cell differentiation. For example, collaborating NIH and Walter Reed Army Medical Center researchers discovered that waste tissue removed surgically to promote the healing of orthopedic injuries and traumatized muscle contains large numbers of progenitor cells that can differentiate into bone, fat, and cartilage cells. This discovery indicates that these tissues can be a new source of cells for a variety of regenerative therapies.[153] In another example, NIH-supported investigators have developed a type of peptide molecule that can "self-assemble" into tiny, highly specialized fibers in experimental animals. The investigators showed that treating the animals with the fibers following experimentally induced spinal cord injury reduced cell death at the injury site and promoted both motor and sensory fiber regrowth.[154] A major collaboration between the NIH intramural program and the Department of Defense on traumatic brain injury (TBI) research is the new Center for Neuroscience and Regenerative Medicine (CNRM). CNRM research programs will focus on the full spectrum of TBI in patients injured in combat and in civilians with TBI. The Center's mission includes catalyzing advances in treatment, rehabilitation, and long-term recovery for individuals experiencing TBI.[155] A major collaboration between the NIH intramural program and the Department of Defense on TBI research is the new Center for Neuroscience and Regenerative Medicine (CNRM). CNRM research programs will focus on the full spectrum of TBI in patients injured in combat and in civilians with TBI. The center's

mission includes catalyzing advances in treatment, rehabilitation, and long-term recovery for individuals experiencing TBI.

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Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Human Development

Environmental Epigenetics: Key Mechanisms for Environmental Effects on Gene Function and Disease: Increasing evidence demonstrates that epigenetic mechanisms—cellular regulatory processes that influence the expression of genes without affecting DNA sequence—play important roles in the pathogenesis of disease. Epigenetic regulation of genes is critically important in normal developmental biology and disease development/progression, and epigenetic modifications can be influenced by environmental exposures (this may be an important mechanism for gene/environment interactions). An early NIH grant program called Environmental Influences on Epigenetic Regulation has resulted in some groundbreaking research on understanding these processes and their roles in health and disease. We know that environmental exposures early in development affect the risk of diseases and dysfunctions that occur in adulthood, many years later. Evidence is growing that exposures *in utero* exert their effects through epigenetic modifications such as DNA methylation (a chemical change to DNA that is associated with silencing gene expression). A recent study in yellow agouti mice demonstrated that maternal exposure to bisphenol A shifted the coat color of the offspring by decreasing methylation in a regulatory portion of the DNA sequence upstream of the coat-color gene. Moreover, maternal dietary supplementation with either folic acid or a phytoestrogen (genistein) inhibited the ability of bisphenol A to reduce DNA methylation. These and other results highlight the importance of this growing area of research for our ability to understand developmental pathogenesis and to design effective interventions.

→ Bjornsson HT, et al. *JAMA* 2008;299(24):2877-83. PMID: 18577732. PMCID: PMC2581898.
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Perera F, et al. *PLoS One* 2009;4(2):e4488. PMID: 19221603. PMCID: PMC2637989.
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Dolinoy DC, Jirtle RL. *Environ Mol Mutagen* 2008;49(1):4-8. PMID: 18172876.
Dolinoy DC. *Nutr Rev* 2008;66 Suppl 1:S7-11. PMID: 18673496. PMCID: PMC2822875.
Patel MM, Miller RL. *Curr Opin Pediatr* 2009;21(2):235-42. PMID: 19663041. PMCID: PMC2740858.
Miller RL. *J Clin Invest* 2008;118(10):3265-8. PMID: 18802486. PMCID: PMC2542856.

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIEHS**)

Discovery of Novel Epigenetic Marks in Mammalian Cells: The NIH Roadmap Epigenomics Program aims to accelerate the promise of epigenetics into applications that affect human health and a wide range of common complex human diseases by fostering the development of novel resources for research in this field. Epigenetics refers to various modifications to DNA, its associated proteins, or overall chromosome structure that influence whether genes are active or silent, independent of the DNA sequence. Research supported by this program will characterize the "epigenome," a catalog of the stable epigenetic modifications or "marks" that occur in the genome (and which may differ in different types of cells) and its impact on health and disease. One component of the program is an initiative to support research to identify novel epigenetic marks in mammalian cells and assess their role in the regulation of gene activity. It is anticipated that the results of these studies will be translated quickly to global epigenome mapping in human cells (conducted by the Epigenomics Roadmap Program's Reference Epigenome Mapping Centers). The eight research grants funded by this component of the program are expected to yield results that could have a significant impact on our understanding of gene regulation in mammals. In the long term, advances in these areas will enhance our ability to investigate, diagnose, and ameliorate human disease with a significant epigenetic component. For instance, NIH plans to build on these studies to examine the role of epigenomics in diabetes complications and to study effects of the intrauterine environment on the development of diabetes. Other research will examine epigenetic markers of beta cell differentiation.

→ For more information, see http://nihroadmap.nih.gov/epigenomics/initiatives.asp
→ This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDDK**, Common Fund - all ICs participate)

Developmental Genomics: Neural tube defects are a class of birth defects affecting the brain and spinal cord. Taking folic acid during the weeks before and after conception greatly can reduce a woman's chances of having a child with a neural tube defect. Still, researchers have not yet fully defined the complex relationship that exists between folic acid and vitamin B12, which is essential for synthesizing DNA during growth and development. Because Ireland has a particularly high rate of neural tube defects, NIH researchers collaborated with Irish researchers to look more closely at the role of vitamin B12 in the developmental disorder. They found that children born to women who have low blood levels of vitamin B12 shortly before and after conception have an increased risk of a neural tube defect. In light of their discovery, researchers said it would be wise for all women of childbearing age to consume the recommended amount of vitamin B12 in addition to folic acid. In a study looking at a different type of birth defect, a trans-NIH team found that about 20 percent of the incidence of isolated cleft lip may be due to a very tiny alteration in a gene involved in facial development. Oral-facial clefts are among the most common birth defects in the United States, arising from disruptions in a dynamic but still poorly understood interplay of genes, diet, and environment.

→ Molloy AM, et al. *Pediatrics* 2009;123(3):917-23. PMID: 19255021.
Rahimov F, et al. *Nat Genet* 2008 Nov;40(11):1341-7. PMID: 18836445. PMCID: PMC2691688.
→ For more information, see http://www.genome.gov/27530477
→ For more information, see http://www.genome.gov/27528380
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Genomics*
→ (E, I) (**NHGRI**, NICHD, NIDCR)

Basic Research on Human Embryonic Stem Cells: Research on human embryonic stem cells (hESC) promises to elucidate critical events in early human development and may revolutionize customized regenerative medicine. Since FY 2007, NIH has funded five Program Projects on the basic biology of hESC and has developed initiatives to support fundamental research on a new kind of stem cell, called induced pluripotent stem cells (iPS). iPS cells are reprogrammed from adult cells to a pluripotent state remarkably like hESC. These reprogrammed cells offer a powerful approach to generating patient specific stem cells that ultimately may be used in the clinic. NIH sponsored the third in a series of workshops on research and future directions in human embryonic stem cell research in September 2009.

→ For more information, see http://www.nigms.nih.gov/Initiatives/StemCells
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIGMS**)

Cell Senescence and Aging: Cell senescence is a mechanism prominent in aging processes and widely considered as an anti-cancer preventive or treatment therapy. Studies focus on such topics as senescence induced by the Ras gene and its potential to halt or slow tumor progression, the role of the retinoblastoma protein pRb in cellular senescence and the development of a wide range of cell types and associated tumors, telomere attrition, the role of oxidative stress, epigenetic regulation, and DNA damage and repair. NIA-supported studies on Werner syndrome (a condition characterized by accelerated aging in children) and the role of the WRN protein in telomere metabolism are improving our understanding of basic cellular mechanisms that act to suppress development of specific aging characteristics and cancer.

→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Research*
→ (E/I) (**NIA**)

Magnetic Resonance Imaging; Study of Normal Brain Development: Understanding healthy brain development is essential to finding the causes of many childhood disorders, including those related to intellectual and developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases. NIH is creating the Nation's first database of MRI measurements and analytical tools, and clinical and behavioral data to understand normal brain development in approximately 500 children from across the Nation. This large-scale longitudinal study uses several state-of-the-art brain-imaging technologies. Anatomical neuroimaging scans; demographic, medical, cognitive, and behavioral data; and magnetic resonance spectroscopy data now are available to the research community via the NIH MRI Study of Normal Brain Development website.

→ For more information, see http://www.bic.mni.mcgill.ca/nihpd/info/index.html
→ This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System
→ (E/I) (**NICHD**, NIDA, NIMH, NINDS) (GPRA)

Life Stages

Baltimore Longitudinal Study of Aging Celebrates 50 Years: In 2008, the world's most comprehensive and longest-running longitudinal examination of human aging celebrated an astonishing 50 years of ground-breaking research that has transformed the field of geriatrics. Since its establishment in 1958, the NIH-supported Baltimore Longitudinal Study of Aging (BLSA) has provided a wealth of information on the physical consequences of aging and has helped distinguish changes due to aging from those due to disease. Over the past 50 years, BLSA scientists have produced a number of notable findings. For example, they found that, contrary to some stereotypes, people don't become progressively cranky, depressed, or withdrawn as they age. In fact, these traits remain relatively stable for adults after age 30. Another significant BLSA finding has been the discovery of the relationship between PSA (prostate-specific antigen) levels and prostate cancer. BLSA scientists also have elucidated the relationship between age-related changes in the arteries and

cardiovascular disease and distinguished normal age-related declines in cognitive ability from those associated with Alzheimer's disease and related conditions.

→ For more information, see http://www.grc.nia.nih.gov/branches/blsa/blsa.htm
→ (I) (**NIA**)

Adolescent Medicine Trials Network for HIV/AIDS (ATN): Although one-third to one-half of new HIV infections occur among adolescents and young adults, researchers know little about how the complex physiological changes associated with adolescence affect the transmission and course of HIV infection. NIH is supporting a national clinical research network to address the unique challenges and clinical management needs of HIV-positive adolescents and those at risk of infection. Researchers in this network are conducting biomedical, behavioral, and community-based studies to ensure that teens can benefit from the most promising preventive and treatment interventions. For example, one recently published study conducted by the ATN documented that HIV-positive adolescents frequently do not follow prescribed treatment regimens, and the study also identified several factors associated with nonadherence to therapy.

→ Rudy BJ, et al. *AIDS Patient Care STDS* 2009;(3):185-94. PMID: 19866536.
→ For more information, see http://www.atnonline.org
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NICHD**, NIDA, NIMH)

Pelvic Floor Disorders: Research supported by NIH showed that nearly one-quarter of all U.S. women were afflicted with one or more pelvic floor disorders. These disorders result when the muscles and connective tissue within the pelvic cavity weaken or are injured, leading to dysfunction of one or more pelvic organs. The NIH-supported Pelvic Floor Disorders Network, with seven sites throughout the country, supports research on the prevention and treatment of pelvic floor disorders. A recent study by the network revealed that a special two-step surgical procedure, compared to standard practice, reduced by half the incidence of urinary incontinence in women with pelvic organ prolapse. In addition, NIH plans to enhance collaborative research among basic scientists and clinician researchers in female pelvic floor disorders, to promote research that has the greatest clinical applicability for addressing unknown aspects of physiology and pathophysiology of pelvic function.

→ For more information, see http://www.pfdnetwork.org/
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-008.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NICHD**, NIDDK, ORWH)

Cesarean Delivery vs. Vaginal Birth: The rate of cesarean delivery has risen dramatically over the past 2 decades; in fact, cesarean delivery currently ranks as the most commonly performed surgical procedure in the United States. More research is needed to determine how frequently cesarean deliveries are scheduled for women without medical indications for the procedure, and how these “maternal request” deliveries compare with vaginal delivery in terms of child and maternal health outcomes. Currently, NIH is supporting a Cesarean Registry through the Maternal-Fetal Medicine Units Network. Using data from the registry, researchers found that newborns are at greater risk for health complications after an early cesarean section delivery. Infants delivered by a repeat elective cesarean section at or after 37 weeks, and before 39 weeks, are at significantly increased risk of breathing problems, blood infection, low blood sugar, and admission to the neonatal intensive care unit, similar to those of infants born preterm. These findings continue to support recommendations that clinicians advise their patients to schedule an elective delivery no sooner than 39 weeks of pregnancy. A cesarean delivery that is not medically necessary before this time puts the infant at increased risk of respiratory problems and other adverse health outcomes.

→ Tita AT, et al. N Engl J Med 2009;360:111-20. PMID: 19129525.

→ For more information, see http://www.bsc.gwu.edu/MFMU/index.html
→ (E) (**NICHD**)

Most, but Not All, Late-talking Toddlers Catch Up: By age 2, children should have a vocabulary of about 50 words and should begin to combine those words in 2- or 3-word sentences. Children with Specific Language Impairment (SLI) are late talkers with normal scores for nonverbal intelligence and no hearing loss. They demonstrate normal motor skills, social-emotional development, and neurological profiles—the only noticeable gap is in language development. NIH-supported scientists studying language emergence have shown that up to 80 percent of children with SLI at age 2 will catch up by age 7. They also noted that boys are three times more likely than girls to be diagnosed with SLI. Yet when the children were 7 years old, no differences were found between girls and boys. The scientists noted that current study methods are unable to predict which children with SLI will fail to "catch up." They now are working to determine how best to identify children with SLI who need intervention and enrichment to successfully close the language delay gap.

→ Rice ML, et al. *J Speech Lang Hear Res* 2008;51(2):394-407.
→ (E) (**NIDCD**)

Pregnancy and Perinatology: NIH continues to support a portfolio of research on high-risk pregnancies and poor pregnancy outcomes, including preterm labor and birth, fetal disorders, Sudden Infant Death Syndrome, maternal health, and stillbirth. Much of this research is conducted through centers and networks that bring together researchers from different disciplines and allow them to study larger numbers of patients. NIH also led the Surgeon General's Conference on the Prevention of Preterm Birth. To immediately implement some key conference priorities, NIH launched a program to identify and address the factors contributing to prematurity among women having their first baby. For those infants born with an adverse pregnancy outcome, NIH plans to support research to develop safe and effective instruments and devices for infants in the neonatal intensive care unit to optimize their care and developmental outcomes. In addition, NIH commissioned an Institute of Medicine (IOM) study to review and update the 1990 IOM recommendations for weight gain during pregnancy. IOM's new pregnancy weight gain guidelines are similar to its 1990 guidelines, except there now is an upper limit on how much weight obese women should gain while pregnant, as gaining too much weight can be risky for both mother and infant.

→ For more information, see http://www.nichd.nih.gov/news/resources/spotlight/040908_preterm_prevention.cfm
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-029.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-018.html
→ (E) (**NICHD**, NHLBI, NIDDK, ORWH)

Newborn Screening: Screening and treating newborns for phenylketonuria and hypothyroidism have virtually eliminated these conditions as a cause of intellectual disability in the United States. NIH recently created a newborn screening translational research network to develop novel technologies and clinical therapies that improve early detection and treatment of newborns with heritable genetic disorders and other congenital conditions. Such a network facilitates and speeds the process by which scientific advances can be translated into clinical practice. Complementing the new research network is an initiative to develop new technologies for newborn screening that can be used to screen for a greater number of conditions than can be screened with current technologies. New technologies would benefit newborn screening programs across the country. In addition, NIH is gathering new data on other conditions, such as Severe Combined Immune Deficiency (a rare form of immune deficiency), to enable researchers to develop screening techniques for this heritable condition.

→ (E) (**NICHD**)

Family Satisfaction During Decisions to Withdraw Life Support: Clinicians in the intensive care unit (ICU) often care for patients who are on several life support measures simultaneously. When such a patient is dying and the decision is reached to withdraw life support, these clinicians may make an imperfect compromise in seeking to balance the complex needs of the patient and the patient's family—they may remove the life support measures one at a time over a period of days, rather than withdrawing all at once. This practice, referred to as sequential withdrawal, may be relatively common, and may have a varying impact on the family's satisfaction with ICU care. The research team examined the life support withdrawal process for 584 patients who died in the ICU or within 24 hours of discharge from the ICU, and surveyed the family members regarding their perceptions of the care provided. When surveyed 1 to 2 months after the death of the patient, family members of patients who had a short ICU stay reported a lower satisfaction with the ICU care if the withdrawal process was extended over more than 1 day. However, for family members of patients who had a long ICU stay (8 days or more), satisfaction with care increased with a more extended duration of the withdrawal. In addition, family satisfaction with care was higher if the patient was off the ventilator at the time of death. Withdrawal of life support is a complex process that depends on patient and family characteristics; however, sequential withdrawal of life support is a frequent phenomenon that sometimes seems to be associated with family satisfaction.

- → Gerstel E, et al. *Am J Respir Crit Care Med* 2008;178(8):798-804. PMID: 18703787. PMCID: PMC2566791.
- → For more information, see http://www.nih.gov/news/health/oct2008/ninr-15.htm
- → For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18703787
- → This example also appears in Chapter 3: *Clinical and Translational Research*
- → (E) (**NINR**)

Researchers Developing a Noninvasive Ultrasound Technique to Detect Early Signs of Premature Delivery: Premature delivery is one of the leading causes of infant mortality in the United States, according to CDC. Currently, clinicians only can attempt to delay delivery once the extensive uterine contractions of labor have been initiated in the final stages of the delivery process. However, because the cervix prepares for delivery weeks to months before labor in a process termed “preterm cervical ripening,” an NIH-supported scientist, together with a team of electrical and computer engineers, theorized that a noninvasive ultrasound technique might be used to detect this early warning sign well in advance of premature delivery. The research team developed and tested such a technique using computer simulations in rat tissue samples, followed by studies with live rats. The results were promising in that cervical changes clearly were identifiable using this technique in the tissue samples. With further development, this innovative technique could prove powerful in identifying mothers at risk for premature delivery, thereby reducing or preventing the associated morbidity and mortality.

- → Bigelow TA, et al. *J Acoust Soc Am* 2008;123(3):1794-800. PMID: 18345867. PMCID: PMC2637349.
- → For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18345867
- → This example also appears in Chapter 3: *Technology Development*
- → (E) (**NINR**)

Addressing the Heterogeneity of Autism Spectrum Disorders: NIH released a series of Funding Opportunity Announcements (FOAs), supported by funds from the American Recovery and Reinvestment Act of 2009, soliciting applications for 2-year research projects to address the heterogeneity of Autism Spectrum Disorders (ASD). This initiative represents the largest NIH funding opportunity for research on ASD to date and will jump-start many of the short-term objectives set forth in the Interagency Autism Coordinating Committee's Strategic Plan for Autism Spectrum Disorder Research. The FOAs target research in areas such as measurement development, biomarkers, immune and central nervous systems interactions, genetics, environmental risk factors, model development, treatment and intervention, and services research.

- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-170.html
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-171.html

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-172.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-173.html
→ For more information, see http://www.nimh.nih.gov/science-news/2009/rising-to-the-challenge-nih-will-use-60-million-in-recovery-act-funds-to-support-strategic-autism-research.shtml
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIMH**, NICHD, NIDCD, NIEHS, NINDS) (ARRA)

Developing Interventions to Improve Palliative Care at the End of Life: The life expectancy of the American people has reached a historic high, but along with increased life expectancy comes an increase in the number of people living with, and dying from, chronic debilitating diseases. Prolonged courses of decline at the end of life, palliative treatment options, and life-sustaining technologies have raised many important research questions within the last decade. In addition, the needs of dying children and their families are coming into greater focus, because death in childhood stands out as a particular tragedy and a unique end-of-life experience for all involved. To address these needs, NIH-supported end-of-life science seeks to understand dying with respect to the needs of dying persons and formal and informal caregivers. It includes research on issues such as: alleviation of symptoms, psychological care, near-death preferences, advance directives, and family decision-making. Likewise, end-of-life research addresses the cultural, spiritual, age-specific, and disease-specific factors that make each person's experience at the end of life unique. In FY 2009, NIH announced a funding initiative to develop and test interventions to enhance end-of-life and palliative care that providers can implement across multiple settings, illnesses, and cultural contexts. NIH made the first awards under this solicitation in late FY 2009.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-09-004.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NINR**, NCI)

Workshop on Late-Life Mental Disorders: In FY 2009, NIH undertook a review and analysis of its research program on geriatric translational neuroscience to identify strengths and gaps in current science, and to identify promising new research targets and strategies. As part of this process, a workshop was held that brought together basic and clinical researchers with expertise in aging and mental health. Workshop participants focused on identifying key research questions related to discovering the causes of mental disorders in older populations; charting mental illness trajectories across later-life stage, so as to provide a better evidence base on when, where, and how to intervene; and building the field's scientific infrastructure through training.

→ For more information, see http://www.nimh.nih.gov/research-funding/scientific-meetings/2009/new-perspectives-in-the-translational-neuroscience-of-late-life-mental-disorders.shtml
→ (E) (**NIMH**)

National Database for Autism Research: The National Database for Autism Research (NDAR) is a collaborative biomedical informatics system created by NIH to provide a national resource to support and accelerate research in autism spectrum disorder (ASD). NDAR hosts human genetic, imaging, and phenotypic research data relevant to ASD, making these data available to qualified researchers. NDAR also has the capability to allow investigators to use NDAR for data sharing among select collaborators in ongoing studies. Through its Data Dictionary, NDAR will foster the development of a shared, common understanding of the complex data landscape that characterizes ASD research. Finally, its architecture facilitates linkage of NDAR with other significant data resources, regardless of their location or ownership and in ways that respect the policies and implementations of those other data resources.

→ For more information, see http://ndar.nih.gov/

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NIMH**, CIT, NICHD, NIDCD, NIEHS, NINDS)

Studies of Diabetes in Youth: NIH and CDC support the SEARCH for Diabetes in Youth study, which is providing key data on childhood diabetes incidence and prevalence. Recent data from SEARCH revealed unexpectedly high rates of diabetes in youth across most ethnic and racial groups in the United States. SEARCH also estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. To address the emerging problem of type 2 diabetes in youth, NIH supports the HEALTHY multicenter study to prevent risk factors for type 2 diabetes in middle-school children. A pilot study for HEALTHY found that an alarmingly high 15 percent of students in middle schools enrolling mainly minority youth had 3 major risk factors for type 2 diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease risk for obesity and diabetes. Thus, NIH launched the HEALTHY study in 2006. Half of the 42 participating middle schools receive the intervention, which includes changes to school food service and physical education classes, behavior change, and communications campaigns. More than 70 percent of the enrolled students are from minority populations. For children who already have been diagnosed with type 2 diabetes, NIH supports the Treatment Options for Type 2 Diabetes in Youth (TODAY) study, which is comparing three different treatment strategies for children with the disease.

→ Mayer-Davis EJ, et al. *Diabetes Care* 2009;32 Suppl 2:S99-101. PMID: 19246580. PMCID: PMC2647691.
→ For more information, see http://www.searchfordiabetes.org/
→ For more information, see http://www.todaystudy.org/index.cgi
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**, CDC)

The Sister Study: Environmental Risk Factors for Breast Cancer: The NIH Sister Study prospectively examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The frequency of relevant genes and shared risk factors is greater among sisters, increasing the ability of the study to detect risks. Researchers will collect data on potential risk factors and current health status, and will collect and bank blood, urine, and environmental samples for future use in studies of women who develop breast cancer or other diseases compared with those who do not. Analysis of new cases will assess the separate and combined effects of environmental exposures and genetic variations that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors like smoking, occupational exposures, alcohol, diet and obesity, and include analysis of phthalates, phytoestrogens, metals, insulin, growth factors, vitamins and nutrients, and genes in blood and urine. The study also allows investigators to examine a wide range of health outcomes of relevance to women, and to create a framework from which to test new hypotheses as they emerge. In addition to its focus on genetic and environmental causes of breast cancer, the prospective Sister Study tracks changes in health status over time. Among the chronic diseases currently studied are uterine fibroids and endometriosis, rheumatoid arthritis and other autoimmune diseases, thyroid disease, asthma, and cardiovascular diseases. As the cohort ages, the Sister Study will address aging-related health outcomes including osteoporosis, Parkinson's disease, and age-related cognitive decline.

→ For more information, see http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E/I) (**NIEHS**, NCMHD)

New Interventions for Menopausal Symptoms: Women going through the menopause transition may experience a variety of symptoms, ranging from vasomotor symptoms (hot flashes and night sweats) to sleep disturbance, mood disorders, loss of sexual desire, and vaginal dryness. As many as two-thirds of all women report vasomotor symptoms, and more than 85 percent report at least 1 menopausal symptom. For the 25 percent of symptomatic women who are burdened severely, the resulting discomfort greatly diminishes their quality of life. Until recently, menopausal hormone therapy (MHT) using estrogen has been the therapy of choice for relieving menopausal symptoms. But after 2002 and the release of findings from the Women's Health Initiative and other studies showing that MHT can be associated with an increased risk of serious health problems such as blood clots, stroke, heart disease, breast cancer and cognitive impairment, women and their health practitioners have been in search of alternative strategies to improve menopausal quality of life. NIH has established the Menopausal Symptoms: Finding Lasting Answers for Sweats and Hot Flashes (MS FLASH) initiative to conduct collaborative studies on interventions for menopausal vasomotor symptoms. A variety of interventions currently are under study, including yoga, exercise, paced respiration, and other hormonal and nonhormonal treatments.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-08-004.html
→ (E) (**NIA**, NCCAM, NICHD, ORWH)

Ginkgo Evaluation of Memory (GEM) Study Shows No Benefit in Preventing Dementia in the Elderly: Dementia is a loss of brain function that causes serious changes in memory, personality, and behavior. Alzheimer's disease, the most common form of dementia in older people, affects as many as 4.5 million Americans. Some people use extracts of leaves from the *Ginkgo biloba* tree in an effort to prevent or treat Alzheimer's and other types of dementia. NIH-supported researchers tested ginkgo in a large sample of older adults to see whether it could prevent or delay the onset of dementia, particularly Alzheimer's. The study enrolled 3,069 participants ages 75 or older who had normal cognition or mild cognitive impairment. For about 6 years, they took twice-daily doses (120 milligrams) of either ginkgo extract or a placebo. The study found that ginkgo did not lower the overall incidence of dementia or Alzheimer's. Nevertheless, the study demonstrates the feasibility of large dementia prevention trials in older adults, and provides useful information about how to design and conduct such trials. The results of this study confirm the importance of randomized trials in determining therapeutic benefit of new approaches to dementia and Alzheimer's disease. The results also provide a wealth of information that will be valuable in designing future clinical trials. Future analyses of the data will provide additional information on ginkgo's possible effects on cardiovascular disease, cancer, depression, and other age-related conditions. They also may identify subgroups at greater risk for developing dementia.

→ Kinlock TW, et al. *J Subst Abuse Treat* 2009;37(3):277-85. PMID: 19017911. PMCID: PMC2823569.
→ For more information, see http://nccam.nih.gov/research/results/gems/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E) (**NCCAM**, NHLBI, NIA, NINDS, ODP/ODS)

Alzheimer's Disease Cooperative Study (ADCS): Much of the AD-related clinical research supported by NIH takes place through the ADCS. The study involves a consortium of centers in the U.S. and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of AD or predict development of the disease in vulnerable people. To date, approximately 4,600 people have participated in the trials. Five new trials are underway through ADCS. These include: (1) a trial to examine whether treatment with DHA, an omega-3 fatty acid, will slow decline in AD; (2) a multicenter trial to evaluate home-based assessment methods for AD prevention research in people age 75 or older; (3) a trial to evaluate the efficacy and safety of 18 months of treatment with the drug PF-04494700 (TTP488), an oral compound formulated to prevent amyloid beta from binding to a specific brain receptor; (4) a trial of valproate, an anticonvulsant drug, to determine its ability to delay the emergence of agitation and psychosis and possibly the clinical progression of AD; and (5) a trial of intravenous immunoglobulin, which contains naturally occurring antibodies against beta-amyloid, to establish its clinical utility for treating AD. This program is a cornerstone of the NIH

GPRA goal to: “By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease.”

→ For more information, see http://www.adcs.org/Default.aspx
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: Clinical *and Translational Research*
→ (E) (**NIA**) (GPRA)

Alzheimer's Disease Neuroimaging Initiative (ADNI): ADNI is an innovative public-private partnership for examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease (AD). ADNI has reached its target enrollment of 800 participants, and supported development of a number of tools and methods now in use in the United States as well as in Japan, the European Union, and Australia. Other expansions include a genome-wide association study of ADNI participants scheduled to provide the most extensive and robust dataset of its kind in the AD field; a study that allows for longitudinal analysis by the collection of additional cerebrospinal fluid from participants over several years; and a study exploring the use of PET and Pittsburgh Compound B (PIB) as a tool for developing biochemical markers. A recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer's and established a method and standard of testing for these biomarkers.

→ For more information, see http://www.loni.ucla.edu/ADNI
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIA**, NIBIB)

Interventions to Remediate Age-Related Cognitive Decline: Age-related cognitive decline distinct from dementia will affect most older individuals to some extent and has a direct impact on their independence and vitality. Cognitive training, physical exercise, enhancement of self-efficacy, social engagement, diet, environmental enrichment, and stress reduction have all been shown to have positive effects on cognition; however, the quality of this evidence varies widely across studies. NIH, in partnership with the McKnight Brain Research Foundation in conjunction with the Foundation for NIH, has initiated a program to convert insights from previous work in cognitive aging into feasible intervention strategies that can be tested in randomized clinical trials. The program's primary goal is to support the initial development and pilot testing of behavioral interventions (individually and in combination) to establish their feasibility, the likely strength of their effects, and immediate and short-term efficacy. These early steps should allow these interventions to move to new clinical trials.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-09-009.html
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIA**)

Translational Research on Alzheimer's Disease (AD): To move basic research on AD and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. A number of agents are undergoing testing, including antihypertensives, anti-inflammatory drugs, and novel small molecules. In addition, in recent years, NIH-supported basic research has contributed to industry development of new Alzheimer's disease drugs. This program is a cornerstone of the NIH GPRA goal to “by 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease.”

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-048.html
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIA**) (GPRA)

Genes Change How We Hear as We Grow Older: Scientists know that genetics play some role in presbycusis (age-related hearing loss), which affects most individuals greater than 60 years old. But until recently, they have been unable to pinpoint any human gene that may be responsible for presbycusis. The search for specific genes involved in presbycusis is complicated because many other factors can contribute to the onset of age-related hearing loss, including sound exposure, medications that can damage hearing, the aging brain, and changes in the sound-detecting cells of the inner ear. A research team of NIH-supported scientists looked at gene activity in the inner ear of a particular strain of mice that serves as a model for presbycusis. The team identified eight genes, all of which were involved in apoptosis (programmed cell death), whose activity increased as mice aged and as hearing loss progressed. Apoptosis is the body's way of getting rid of cells that are damaged or no longer needed. Increased or abnormal apoptosis, however, also is involved in many disease processes. The new research is the first demonstration that increased apoptosis also occurs in the aging inner ear. This research offers a potential new area of discovery as scientists work to prevent and even reverse age-related hearing loss. Presbycusis may be treated one day by a drug that stops or delays the sound-detecting cells in the inner ear from undergoing apoptosis as they age.

→ Tadros SF, et al. *Apoptosis* 2008;13(11):1303-21.
→ For more information, see http://www.nidcd.nih.gov/health/hearing/presbycusis.asp
→ (E) (**NIDCD, NIA**)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects adipose tissue and alters hormonal control of sexual maturation. Endocrine distruptors, irradiation, and psychosocial elements also will be studied for effects.

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Egeblad M, et al. *Dis Model Mech* 2008;1(2-3):155-67; discussion 165. PMID: 19048079. PMCID: PMC2562195.
Aupperlee MD, et al. *Endocrinology* 2009;150(3):1485-94. PMID: 18988671. PMCID: PMC2654739.

Lu P, et al. *Dev Biol* 2008;321(1):77-87. PMID: 18585375. PMCID: PMC2582391.
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Teitelbaum SL, et al. *Environ Res* 2008;106(2):257-69. PMID: 17976571.
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Santos SJ, et al. *J Steroid Biochem Mol Biol* 2009;115(3-5):161-72. PMID: 19383543. PMCID: PMC2729057.
Yang C, et al *Reprod Toxicol* 2009;27(3-4):299-306. PMID: 19013232.
Smith SW, et al. *J Health Commun* 2009;14(3):293-307. PMID: 19440911. PMCID: PMC2718320.
J Health Psychol 2008;13(8):1180-9. PMID: 18987091.
Atkin CK, et al. *J Health Commun* 2008;13(1):3-19. PMID: 18307133.
Kariagina A, et al. *Crit Rev Eukaryot Gene Expr* 2008;18(1):11-33. PMID: 18197783.
Medvedovic M, et al. *Physiol Genomics* 2009;38(1):80-8. PMID: 19351911. PMCID: PMC2696152.
Biro FM, et al. *J Pediatr Adolesc Gynecol* 2009;22(1):3-6. PMID: 19232295. PMCID: PMC2744147.

→ For more information, see http://www.bcerc.org/
→ This example also appears in Chapter 2: *Cancer*, Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIEHS**, NCI) (GPRA)

Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE): A large body of research in animals indicates that substantially reducing caloric intake while maintaining optimal nutrition can significantly lengthen life span. The CALERIE study will help to determine if these effects extend to humans. This long-term study began in January 2007 and is ongoing. Recently, CALERIE researchers used state-of-the-art techniques to measure metabolic changes that occur in response to caloric restriction with or without exercise. They found that energy metabolism slows in response to caloric restriction, but the addition of exercise to a caloric restriction regimen may forestall such a "metabolic adaptation," potentially explaining why a combination of dietary restriction and exercise, as opposed to dietary restriction alone, may be the best intervention to sustain weight loss. Overall, these findings provide important information about the mechanisms of weight loss and indicate that exercise may be an important component of a weight loss regimen.

→ For more information, see http://calerie.dcri.duke.edu
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIA**)

A Variety of Approaches Help Children Overcome Auditory Processing and Language Problems: Almost 7 percent of school-age children have difficulties learning and using language. Childhood language impairments can have lifelong effects on an individual's social life, academic career, and job aspirations. Each year, more than 1 million public school children receive interventions to address their language impairments. One very popular intervention is a commercially available software program called Fast ForWord Language (FFW-L; Scientific Learning Corporation, 1998). NIH-supported scientists conducted a randomized controlled trial of more than 200 children with language impairments, to assess whether those who used FFW-L had greater improvement in language skills than those who used one of two other methods, plus an active control group. The children in all three intervention groups demonstrated statistically significant improvement in both auditory processing and language skills. Thus, FFW-L did not provide a significant advantage over other types of interventions delivered in a similar intensive manner. Surprisingly, children in the active control group, which received individualized attention, instruction, and computerized testing on academic subjects but did not receive language intervention, also demonstrated significant improvement in auditory processing and language skills. This study demonstrated that all four methods improved the children's auditory processing and language skills. The data suggest that intensive programs focusing individualized attention on children with language impairments can improve language skills and preempt lifelong communication difficulties.

→ Tager-Flusberg H, Cooper J. *J Speech Lang Hear Res* 1999;42:1275-8. PMID: 10515521.
Gillam RB, et al. *J Speech Lang Hear Res* 2008;51(1):97-119. PMID: 18230858. PMCID: PMC2361096.
→ For more information, see http://www.nidcd.nih.gov/news/releases/08/01_30_08.htm

→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDCD**, NICHD)

Brain Matures a Few Years Late in ADHD: NIH-supported research on brain development in children with attention-deficit/hyperactivity disorder (ADHD) showed a normal pattern of brain development, but with a striking delay in cortical maturation. Between ages 5 and 15, the maturation of the prefrontal cortex was found to be delayed by roughly 3 years in children with ADHD compared to age-matched children without the disorder. Current studies now are exploring the effects of treatment on the rate of cortical maturation.

→ Shaw P, et al. *Proc Nat Acad Sci U S A* 2007;104(49):19649-54. PMID: 18024590. PMCID: PMC2148343.
→ For more information, see http://www.nimh.nih.gov/science-news/2007/brain-matures-a-few-years-late-in-adhd-but-follows-normal-pattern.shtml
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (I) (**NIMH**)

Centers in Self-Management or End-of-Life Research: Future progress in improving the ability of those with chronic disease at all stages of life to manage their own illness, as well as improving the care of patients at the end of life, will require the development of enhanced research capacity, including more trained investigators and expanded institutional resources. In early 2007, NIH solicited applications for the Centers in Self-Management or End-of-Life Research. These Centers are expected to serve as a nexus for the emergence of self-management and end-of-life research as interdisciplinary sciences. They will train investigators from multiple backgrounds and leverage collaborations to increase the quantity and quality of innovative, interventional research projects. To date, six grants have been awarded from this solicitation. These Centers focus on a variety of topics, such as the self-management of chronic illnesses in Hawaii, biobehavioral research in self-management of cardiopulmonary disease, evidence-based practice in the underserved, and end-of-life transition research.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-004.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-005.html
→ (E) (**NINR**)

Childhood and Maternal Obesity: As the maternal and childhood obesity epidemic widens, researchers are trying to understand the interaction among the many complex biological and behavioral factors that contribute to this rise, identify the long-term impact on mother and child, and develop effective interventions to reverse these trends. NIH obesity research, which includes a range of racial and ethnic groups, is examining such topics as:

- Basic research on the physiology, psychology, and genetics of obesity in children.
- Developing community-based partnerships to prevent and control childhood obesity.
- Applying computational and statistical methodologies to design and analyze multilevel studies on childhood obesity. Multilevel studies include those that consider the range of biological, family, community, sociocultural, environmental, policy, and macro-level economic factors that influence diet and physical activity in children.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-09-140.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-023.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E/I) (**NICHD**, NCI, NHLBI, OBSSR)

Comparative Effectiveness of Treatments for Common Childhood Eye Disorder: Convergence insufficiency (CI) is a relatively common vision problem that develops in childhood in which the eyes do not naturally turn inward when

focusing on a close-up visual target. Symptoms include eye strain, blurred vision, headaches, and discomfort. CI can adversely affect reading ability and reading comprehension and can have a serious impact on an individual's performance in school, career, and quality of life. Eye care professionals treat CI with various forms of eye exercises, done at home or in the office of a trained therapist, that require children to sustain focus on nearby objects. The Convergence Insufficiency Treatment Trial (CITT) compared the effectiveness of these therapies. Results indicate that the most popular treatment, known as home-based pencil push-up therapy, was no more effective in improving patient's symptoms than a placebo therapy. However, 73 percent of children assigned to a regimen of intensive, office-based therapy combined with home reinforcement did improve significantly compared to the placebo group. Other commonly prescribed home-based regimens also showed some benefit but were only about half as successful as office-based therapy with home reinforcement. Although home-based treatments for CI are appealing because of their simplicity and low cost, these results indicate that office-based treatment combined with home reinforcement is more effective in helping children to achieve normal vision and reducing symptoms.

- → Convergence Insufficiency Treatment Trial Study Group. *Arch Ophthalmol* 2008;126(10):1336-49. PMID: 18852411. PMCID: PMC2779032.
- → For more information, see http://archopht.ama-assn.org/cgi/content/full/126/10/1336
- → This example also appears in Chapter 3: *Clinical and Translational Research*
- → (E) (**NEI**)

Comparative Effectiveness Study of Drugs for Age-Related Macular Degeneration: Lucentis was approved by FDA in 2006 for treatment of advanced age-related macular degeneration (AMD), a leading cause of vision loss in older Americans. Though the drug is safe and effective, it is expensive—approximately $2,000 per month—and repeated injections are required. Avastin is a similar pharmaceutical but is far less expensive—approximately $100 per month—and also has been used extensively in treating patients with AMD. Most retinal specialists think that Avastin is a safe and effective alternative to Lucentis. To resolve this question, NIH is funding the Comparison of AMD Treatments Trial (CATT), a multicenter, randomized, clinical trial to compare the safety and efficacy of Avastin and Lucentis, and to explore less-frequent treatment schedules for both drugs. The first participants were randomized in early 2008. If Avastin proves to be comparable to Lucentis, the cost savings could reach $2-3 billion per year. Less frequent treatment schedules also would lower costs, reduce treatment risk, and improve patient quality-of-life.

- → For more information, see http://www.nei.nih.gov/news/pressreleases/022208.asp
- → This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- → (E) (**NEI**)

Demographic and Economic Studies of Aging: NIH supports a number of studies on the demographic and economic changes in our society. The Health and Retirement Study (HRS) is the leading source of combined data on health and financial circumstances of Americans over age 50 and a valuable resource to follow and predict trends and help inform policies for an aging America. Now in its 16th year, the HRS follows more than 20,000 people at 2-year intervals and provides researchers with an invaluable and growing body of multidisciplinary data on the physical and mental health of older Americans, insurance coverage, finances, family support systems, work status, and retirement planning. Recently, researchers used HRS data on memory and judgment of a large subset of HRS participants to determine trends in cognitive status of those age 70 and older. The researchers found that cognitive impairment dropped from 12.2 percent in 1993 to 8.7 percent in 2002. The study recently has been expanded to include additional key constructs in cognitive aging. NIH also has renewed its program of Centers on the Demography and Economics of Aging to foster research in the demography, economics, and epidemiology of aging and to promote the use of important datasets in the field. The achievements of this program in past years were recognized in September 2008 by the Heidelberg Award for Significant Contributions to the Field of Gerontology, a triennial international competition.

→ For more information, see http://hrsonline.isr.umich.edu
→ For more information, see http://agingcenters.org
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIA**)

Detection, Treatment, and Survivorship of Childhood Cancers: NIH has several ongoing programs to improve detection and treatment of childhood cancers, including the work of the NCI Pediatric Oncology Branch, the Childhood Cancer Survivors Study, and the Pediatric Brain Tumor Consortium. Several of these programs are in collaboration with the Children's Oncology Group (COG). A recent COG study discovered that genetic alteration of the IKZF1 gene is associated with very poor outcomes in patients with B-cell progenitor acute lymphoblastic leukemia (ALL). These results should improve risk stratification for ALL patients, helping to ensure that those with high-risk disease receive treatment of appropriate intensity and sparing low-risk patients unnecessary toxic effects. The Therapeutically Applicable Research to Generate Effect Targets (TARGET) initiative is cataloguing alterations in gene expression, gene sequences, and copy number of chromosome segments in pediatric cancers to discover cancer-specific changes. TARGET data are made available to the research community through a Web portal. TARGET researchers have discovered genomic alterations in pediatric ALL that are predictive of relapse and have identified activating mutations in a tyrosine kinase gene family for which small molecule inhibitors are available. Neuroblastoma TARGET specimens were used to confirm that approximately 10 percent of high-risk neuroblastoma cases have activating mutations in another tyrosine kinase, and a pediatric Phase I trial of an inhibitor of this kinase has been developed. The success of the TARGET approach in identifying novel therapeutic targets for ALL and neuroblastoma supports extension of this approach to other childhood cancers.

→ For more information, see http://www.cancer.gov/cancertopics/coping/childhood-cancer-survivor-study
→ For more information, see http://www.survivorshipguidelines.org
→ For more information, see http://home.ccr.cancer.gov/oncology/pediatric/
→ For more information, see http://www.pbtc.org/
→ For more information, see http://www.cancer.gov/NCICancerBulletin/NCI_Cancer_Bulletin_031808
→ For more information, see http://target.cancer.gov
→ This example also appears in Chapter 2: *Cancer*
→ (E/I) (**NCI**) (ARRA)

Epidemiologic Studies of Osteoporosis: NIH supports several prospective cohort studies, including the Study of Osteoporotic Fractures (SOF) in women and Mr. OS, a study of osteoporosis and other age-related diseases in men. The studies, which have been underway since 1986 and 1999, respectively, identified characteristics associated with fracture risk in older Americans. Assessing risk is important because the devastating consequences of low bone mass can be prevented. For example, simple changes to a person's home (e.g., adding more lights, removing clutter) can prevent falls. A balanced diet and modest exercise build bone strength, and medications can slow disease progression. SOF, Mr. OS, and other studies are providing information about osteoporosis diagnosis, treatment, and prevention. SOF and Mr. OS reinforced a notion, outlined in the Surgeon General's 2004 report on Bone Health and Osteoporosis, that older people who have a fracture should be tested for osteoporosis—even if the fracture occurred because of a traumatic injury (e.g., a fall off a ladder or an auto accident) that could hurt a healthy young person. Mr. OS is generating data that the U.S. Preventive Services Task Force can incorporate into guidance on using bone mineral density to assess fracture risk. Scientists using data from the Framingham Osteoporosis Study recently reported that men and women who consumed the most vitamin C had fewer hip fractures than those who consumed less vitamin C—a finding that may have implications for the recommended intakes established for vitamin C. Women's Health Initiative investigators demonstrated that low blood levels of vitamin D, which helps the body absorb calcium from food, also is associated with hip fracture risk.

→ Cawthon PM, et al. *J Bone Miner Res* 2009;24(10):1728-35. PMID: 19419308. PMCID: PMC2743283.
Cauley JA, et al. *Ann Intern Med* 2008;149(4):242-50. PMID: 18711154. PMCID: PMC2743412.

Mackey DC, et al. *JAMA* 2007;298(20):2381-8. PMID: 18042915.
Sahni S, et al. *Osteoporos Int* 2009;20(11):1853-61. PMID: 19347239. PMCID: PMC2766028.

→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/11_28.asp
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/low_vitD_hip_fracture.asp
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIAMS**, NCRR, NHLBI, NIA)

Fetal Alcohol Effects: The developing embryo and fetus is very vulnerable to the adverse effects of alcohol. Since Fetal Alcohol Syndrome was first recognized around 1970, NIH has supported research on outreach to pregnant women for identification and intervention of risky drinking; research to enhance our ability for early identification of and interventions with prenatal alcohol-affected children; research exploring nutritional and pharmacological agents that could lessen alcohol's adverse effects on the developing embryo/fetus; and research on how alcohol disrupts normal embryonic and fetal development. For example, a recent study with rats showed that choline, an essential nutrient, was found to effectively reduce the severity of some fetal alcohol effects, even when administered after the ethanol insult was complete. NIH also is investing in a large-scale prospective study looking at prenatal alcohol exposure along with other maternal risk factors in adverse pregnancy outcomes. Following a 3-year feasibility study, NIH established the Prenatal Alcohol, Sudden Infant Death Syndrome, and Stillbirth (PASS) Research Network, a multidisciplinary consortium to determine the role of prenatal alcohol exposure and other maternal risk factors in the incidence and etiology of sudden infant death syndrome (SIDS), stillbirth, and fetal alcohol syndrome, all of which are devastating pregnancy outcomes. The PASS study prospectively will follow 12,000 pregnant, high-risk, American Indian and South African women and their infants until the infants are 12 months old. Maternal, fetal, and infant measures and tissues will be obtained for analysis.

→ For more information, see http://www.nichd.nih.gov/research/supported/pass.cfm
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIAAA, NICHD**)

Following up on the Multimodal Treatment Study of Children with ADHD (MTA): Children with attention deficit hyperactivity disorder (ADHD), the most common of the psychiatric disorders that appear in childhood, often raise great concern from their parents and teachers because of their inability to focus on or finish tasks. Over time, these children may develop other emotional problems, including mood disorders, loss of self-esteem, and substance abuse. To address these issues, NIH is sponsoring an ongoing, multisite, follow-up of children from the MTA study—a treatment trial of nearly 600 ADHD-diagnosed elementary school children. Findings from the original MTA showed that long-term combination treatment (medication and psychosocial/behavioral treatment), as well as medication-management alone, significantly were superior to intensive behavioral treatments and routine community care in reducing ADHD symptoms. In the follow-up study (n = 485 10 to 13 year olds), children from this cohort and others who received similar pharmacotherapy were assessed for substance abuse outcomes. The study found that despite treatment, children with ADHD showed significantly higher rates of delinquency and substance abuse. Follow-up of the MTA sample is continuing as the participating children go through adolescence and enter adulthood.

→ Molina BS, et al. *J Am Acad Child Adolesc Psychiatry* 2009;48(5):484-500. PMID: 19318991.
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0028.html
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0029.html
→ For more information, see http://www.nida.nih.gov/ResearchReports/comorbidity/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIDA**, NIMH)

Insights into the Molecular Interplay Governing Formation of Cranial Sensory Ganglia: The developmental biology underlying sensory nerve development is fascinatingly intriguing. Take the trigeminal ganglion, which is responsible for touch, pain, and temperature sensation for most of the face. How do precursor cells self-organize in the embryo to produce an anatomically correct sensory network connecting to the central nervous system? Many of the answers are wired into the molecular circuitry of two transient embryonic cell types called neural crest cells and ectodermal placodes. They interact during embryonic development to differentiate into the nerve cells that form the trigeminal ganglion. But virtually nothing is known about the molecular interplay that mediates this interaction. It is a biological puzzle with no known pieces. Now NIH grantees have introduced the first two pieces of the puzzle. They demonstrated in animal studies that the cranial subtype of neural crest cells express the protein Slit1 on their surface during their programmed migration to the trigeminal-forming ectodermal placodes. Meanwhile, as the trigeminal placode cells follow their developmental program, they express on their surface the Robo2 protein, which is the receptor for the Slit1 protein. The Robo2-Slit1 connection, like fitting a hand in a glove, mediates the interaction of neural crest and trigeminal placode cells during the formation of sensory ganglia. When the scientists disrupted one or both molecular signals, the resulting sensory ganglia were abnormal. The teams' findings are important to understanding the mechanisms that regulate formation of the sensory nervous system and thus provide potential targets for identifying the causes of congenital sensory disorders involving the neural crest cell population.

- → Shiau CE, et al. *Nat Neurosci* 2008;11(3):269-76. PMID: 18278043.
- → For more information, see http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/Archive/archive2008/April/TrigeminalGanglion.htm
- → For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18278043?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
- → This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
- → (E) (**NIDCR**)

Intellectual and Developmental Disabilities: Intellectual and developmental disabilities (IDD) have serious, life-long effects on cognitive and adaptive development. NIH supports research to improve functioning for individuals who have IDD and to understand the underlying genetic processes to prevent these conditions. For example, NIH supports 14 IDD Research Centers to advance diagnosis, prevention, treatment, and amelioration of IDD. Because the centers have developed core research resources in genetics, proteomics, and clinical infrastructure, they also provide support for researchers in the Fragile X Syndrome (FXS) Research Centers, Rare Disease Cooperative Centers, and Autism Centers. NIH-supported researchers also are conducting a new study to design and prepare to implement a large multistate study of infants with FXS and their families. The research project goal is to determine the incidence of FXS in the United States, develop screening procedures, address ethical and practical issues related to screening status, and conduct studies on infant development and family adaptation. Also, NIH recently developed a Down syndrome research plan to advance our understanding and speed development of new treatments for the condition—the most frequent genetic cause of mild-to-moderate intellectual disability and associated medical problems.

- → For more information, see http://www.nichd.nih.gov/about/org/cdbpm/mrdd/supported/index.cfm
- → For more information, see http://www.nichd.nih.gov/news/resources/spotlight/012208_research_plan_down_syndrome.cfm
- → (E) (**NICHD**, NCI, NHLBI, NIA, NIAID, NIDA, NIDCD, NIDCR, NIMH, NINDS)

Learning Math and Science: Educators, university leaders, and scientists have called for evidence-based interventions to improve U.S. students' understanding and achievement in mathematics, science, engineering, and technology (STEM). NIH is committed to discovering how children learn and use knowledge, what factors enable this learning, and what can derail learning and/or cause learning disabilities. The NIH Mathematics and Science Cognition and Learning program supports both basic and intervention research in all aspects of quantitative learning, mathematical thinking, and problem-

solving, as well as disorders of impaired math learning. Similarly, NIH supports research in how children and adults develop scientific reasoning and learn scientific principles, and how they choose science- and math-based explanations of real-world events over other explanations. To maintain U.S. leadership in technological advances around the world, research on factors that affect the selection of and advancement in STEM vocations also is being supported. Also, in partnership with other relevant Federal agencies, such as the Department of Education and the National Science Foundation, NIH participates in a national mathematics and science initiative and advises on the best use of scientifically based research on teaching and learning these critical subjects.

→ For more information, see http://www.nichd.nih.gov/about/org/crmc/cdb/prog_mscld/index.cfm
→ (E) (**NICHD**)

Preventing Drug Abuse in Children and Adolescents: Intervening early to reduce risk factors for drug abuse and related problem behaviors can have tremendous impact and improve the trajectory of a young life. NIH is using a multipronged approach to achieve more effective substance abuse prevention by: (1) developing novel strategies, (2) exploring long-term and crossover effects of proven programs, and (3) improving adoption and implementation of evidence-based approaches. Innovative ideas being explored include physical activity to counter drug use, interactive Web-based technologies to engage young people, and brain imaging results to better target media messages. NIH also is building on proven methods such as universal prevention programs, which can reduce an array of risk behaviors, including substance abuse. These programs typically target behaviors appropriate to a child's developmental stage and have been shown to achieve long-term effects. For example, fifth graders who participated in the school-based prevention program "Positive Action" as first graders were about half as likely to engage in substance abuse, violent behavior, or sexual activity as those who did not. Similarly, exposure to the "Good Behavior Game," designed to reduce aggressive, disruptive behavior in first and second grade classrooms, led to fewer drug and alcohol disorders, lower rates of regular smoking, less antisocial personality disorder, and reduced delinquency and violent crime in young adults. However, the development of evidence-based prevention programs is meaningless unless they are adopted by communities. Therefore, NIH also is striving to increase implementation of successful prevention approaches in U.S. schools and communities.

→ Beets MW, et al. *Am J Public Health* 2009;99(8):1-8. PMID: 19542037.
Kellam SG, et al. *Drug Alcohol Depend* 2008;95 Suppl 1:S5-S28. PMID: 18343607. PMCID: PMC2512256.
Spoth R, et al. *Am J Prev Med* 2007;32 (5):395-402. PMID: 17478265.
→ For more information, see http://www.nida.nih.gov/scienceofaddiction/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**)

Promising Clinical Trials of Gene Transfer for Severe Childhood Eye Disease: Leber congenital amaurosis (LCA) is an early-onset, severe retinal disease that results from mutations in any 1 of 13 genes. One form of LCA results from mutations in a gene called RPE65. In 1993, NIH intramural scientists discovered that RPE65 plays a key role in the visual cycle, the set of biochemical interactions that converts light into an electrical signal to initiate vision. Mutations in RPE65 were found to disrupt the visual cycle, resulting in LCA and blindness. Retinal cells in children with LCA remain viable for several years, providing a window of opportunity to intervene therapeutically. An NIH-supported Phase I clinical trial of RPE65 gene transfer in LCA found the treatment is safe and that visual function improved. Two other independent Phase I clinical trials of RPE65 gene transfer also found evidence of visual improvement, but further work is needed to develop the therapeutic potential fully. Ongoing studies are exploring the range of therapeutic doses in adult and adolescent patients as well as rigorous evaluation of the effectiveness of this treatment. Gene transfer is particularly well-suited to the treatment of eye disease. This clinical trial is an important step in treating LCA and in establishing proof-of-concept for gene transfer as a viable therapy for eye disease.

→ Cideciyan AV, et al. *Proc Natl Acad Sci U S A* 2008;30;105(39):15112-7. PMID: 18809924. PMCID: PMC2567501.

→ For more information, see http://www.pnas.org/content/105/39/15112.long
→ For more information, see http://www.nei.nih.gov/lca/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NEI**)

Providing Science-Based Oral Health Information: NIH provides science-based oral health information tailored to meet specific needs. Two examples are described here.

- *Practical Oral Care for People with Developmental Disabilities*: Finding dental care in the community is challenging for people with developmental disabilities. Many dentists do not feel trained sufficiently to provide services to people with special needs. To help increase access to dental care, NIH developed a series of publications to equip general dentists with information they need to deliver quality oral care to persons with developmental disabilities. The series includes continuing education (CE) programs for dentists and dental hygienists and a guide for caregivers describing their important role in maintaining good oral health for their family member or client. The modules are so popular that NIH has extended the CE credit through 2011.
- *Spanish-Language Oral Health Website*: The Special Care Dentistry Association partners with NIH in this important health education outreach—Spanish-Language Oral Health Website. This new Spanish-language website tailored for U.S. Hispanics/Latinos increases Spanish speakers' access to science-based oral health information. The site recently was tested in two cities; participants were Spanish-dominant and bilingual Latinos with backgrounds from different countries of origin and with varying levels of education. The test was to ensure the new website is understandable, credible, and attractive to the intended audience. Other goals included understanding the approach Latinos take when seeking health information online, what they think of the quality of online health information, and whether there are significant differences between Spanish-dominant and bilingual individuals.

→ For more information, see http://www.nidcr.nih.gov/OralHealth/Topics/DevelopmentalDisabilities/
→ For more information, see http://www.nidcr.nih.gov/espanol
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (O) (**NIDCR**, NICHD)

Researchers Discover Why Mammalian Teeth Form in a Single Row: Why do mammals develop a single row of teeth whereas other vertebrates, such as sharks, can develop multiple rows of teeth? Researchers studying mutations in the genes of mice that develop teeth serving no apparent function may have solved the mystery. Most of the mutations under study caused the mice to develop the extra teeth within the space between the normal incisor and the normal first molar. Since tooth buds normally develop within this part of the developmental field but later regress, these genetic alterations did not alter the normal plane within which teeth developed. However, one particular mutation had a different result. The researchers found that a knockout mutation (i.e., elimination) of a gene known as Odd-skipped related 2 (Osr2) also resulted in the production of extra teeth, but strikingly, these teeth developed outside the usual plane, on the tongue side of the normal molars, suggesting that the mutation results in an expansion of this developmental field in the affected mice. Supporting this theory, the knockout mice (i.e., mice lacking Osr2) have spatially expanded expression of other genes involved in tooth development. That suggests that normal Osr2 acts to restrict tooth development to within its usual, single-row plane. Previous work from this group discovered the Osr2 gene and demonstrated that it is a novel regulator of palate formation. The current study demonstrates that Osr2 function also is critical to the patterning of tooth formation and sheds light on the restriction of teeth to a single row in mammals. Osr2 function may be an important consideration for researchers seeking to grow replacements eventually for lost teeth in adults.

→ Zhang Z, et al. *Science* 2009;323:1232-4. PMID: 19251632. PMCID: PMC2650836.
→ For more information, see http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/CurrentSNIB/March/SingleRow.htm

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NIDCR**)

Scientists Demonstrate Hematopoietic Stem Cells' Role in Forming the Stem Cell Niche: Stem cells are important in all multicellular organisms because they have the ability to develop into different kinds of specialized cells. Outside of the organism, researchers can grow stem cells in specific cultures and observe the development of specialized cells. Blood-forming stem cells, known as hematopoietic stem cells (HSCs), are controlled by the hematopoietic stem cell niche, which is located in the bone marrow. Bone-forming cells called osteoblasts are known to play a central role in establishing the HSC niche; however, it is unclear whether HSCs in turn control the differentiation of stem cells that become osteoblasts. Although such interactions in the niche have been proposed, at present there is insufficient direct experimental evidence to define the relationship between HSCs and osteoblast formation. In this work, a group of investigators addressed the role of HSCs in the differentiation of osteoblasts. Using mice, they co-cultured HSCs with stem cells that become osteoblasts, and demonstrated that HSCs can indeed affect the differentiation of cells into osteoblasts. Further, the investigators found that the specialization or differentiation into osteoblasts could be influenced by the age and physical condition of the mice. These findings suggest that HSCs may serve as an important therapeutic target for controlling bone formation and repair. In particular, it should be possible to develop therapeutic agents that specifically target HSCs for treatment of a variety of bone defect such as osteoporosis, nonhealing bone and tooth defects, and congenital bone abnormalities.

→ Jung Y, et al. *Stem Cells* 2008;26(8):2042-51. PMID: 18499897.
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDCR**)

The Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development: An estimated 20 million children under 5 are severely malnourished, leaving them more vulnerable to illness and early death, according to the World Health Organization. Poor nutrition in early childhood may lead to cognitive defects and poor physical development, may increase susceptibility to and severity of infections, and may diminish the effectiveness of childhood vaccines. Focusing on the interactions between communicable and noncommunicable conditions, in 2009, the Foundation for the National Institutes of Health, together with NIH, launched a 5-year study to investigate the links between malnutrition and intestinal infections and their effects on children in the developing world. With the establishment of this remarkable public-private partnership, the project aims to shed light on critical questions related to the interaction between infections and growth and development. This large-scale, Gates-funded, NIH-led, $30 million project will support collaborative, multisite studies of malnutrition and enteric infections involving sites in Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa, and Tanzania. In addition to making critical discoveries that will help save the lives of the world's youngest and poorest children, the main objective of this research network is to create a standardized set of epidemiological tools to accurately study the links between intestinal infections and gut physiology as risk factors for malnutrition across a number of diverse sites in the developing world. This research effort will be conducted in collaboration with universities in the United States and institutions in the developing world.

→ For more information, see http://origem.info/malnutritionstudy/
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (O) (**FIC**, FNIH)

The Role of Development in Drug Abuse Vulnerability: NIH supports animal, clinical, and epidemiological research across the lifespan to examine how developmental stage may influence drug abuse vulnerability or protection. The discovery of a protracted period of brain changes during early development and beyond has been critical to understanding the role of brain maturation in decision-making processes and responses to stimuli, including early (e.g., in utero) exposure to drugs. Adolescence has emerged as a particularly vulnerable period, during which an immature brain circuitry can

translate into a preponderance of emotional reactivity (vs. higher cognitive control) that gives rise to the impulsive characteristics of many teenagers. This in turn may lead to dangerous risk-taking, such as experimenting with drugs that ultimately can lead to addiction. Using both animal models and clinical research, scientists are beginning to understand how environmental variables can play a key role in shaping brain maturation trajectories. In this regard, imaging, genetic, and epigenetic tools are helping interpret the effects of myriad environmental influences, such as quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics on brain development and behavior. In addition, the field of social neuroscience is harnessing the power of multidisciplinary approaches to tease apart these multilevel phenomena to better understand, for example, the neural mechanisms of peer pressure, the connections between chronic stress and risk of drug abuse initiation, and the impact that different early rearing environments can have on gene expression and behavior.

- → For more information, see http://www.nida.nih.gov/tib/prenatal.html
- → For more information, see http://www.nida.nih.gov/scienceofaddiction/
- → This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Molecular Biology and Basic Research*
- → (E) (**NIDA**, NICHD) (GPRA)

Underage Drinking Research Initiative: In 2004, NIH launched its Underage Drinking Research Initiative with the goal of obtaining a more complete and integrated scientific understanding of the environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence—all framed within the context of overall human development. Activities and accomplishments in 2008 and 2009 include: (1) working with the Office of the Surgeon General to disseminate *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking*, including state roll-outs in Oklahoma, Ohio, Nebraska, Wyoming, Montana, Maryland, and Rhode Island (in addition to the six held in 2007); (2) continuing to convene scientific meetings of experts to advance underage drinking research. A series of meetings focusing on the development of guidelines and recommendations for screening children and adolescents for risk for drinking, alcohol abuse, and alcohol use disorders continued in 2008-2009; (3) issuing RFAs and program announcements (PAs), including "Limited Competition: Underage Drinking: Building Health Care System Responses (Phase II)" (RFA-AA-09-001) and "Alcohol, Decision-Making, and Adolescent Brain Development" (PA- 09-097 (R01) and PA-09-096 (R21)); (4) published "A Developmental Framework for Underage Alcohol Use"; and (5) published a *Pediatrics* supplement of seven developmentally focused papers covering a broad range of underage drinking topics.

- → A Developmental Perspective on Underage Alcohol Use. *Alcohol, Research and Health* 2009;32(1). Available at: http://pubs.niaaa.nih.gov/publications/arh321/toc32-1.htm.
  Masten AS, et al. *Pediatrics* 2008;121 Suppl 4:S235-51. PMID: 18381492. Available at: http://pediatrics.aappublications.org/cgi/reprint/121/Supplement_4/S235.
- → For more information, see http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm
- → This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- → (E, O) (**NIAAA**)

Building a Longitudinal Mental Health Tracking System: NIH has laid the initial groundwork to develop a mental health tracking system that will provide epidemiologic information on mental disorders on a continuing basis. By working with Federal agencies that currently conduct large-scale, ongoing national surveys, and adding detailed measures of mental health status, functioning, and service use, NIH will leverage existing resources to collect important mental health information in a cost-efficient manner. The longitudinal nature of the resulting data will provide NIH the ability to track the prevalence, incidence, severity, correlates, and trajectories of mental disorders, as well as related service use and outcomes, over time. The resulting data also could provide important information on key subgroups (e.g., racial/ethnic

populations, people with autism) and geographic areas of varying sizes (e.g., states, counties). These data are critical for targeting future research activities and ensuring the effectiveness of delivered interventions.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIMH**)

EARLI, the Early Autism Risk Longitudinal Investigation: EARLI, the Early Autism Risk Longitudinal Investigation, comprises a network of leading autism researchers from three regions across the country. EARLI is following a cohort of 1,200 mothers of children diagnosed with autism who are pregnant or planning a pregnancy. The EARLI network will study how genetics and environmental factors work together to cause autism by studying families who already are affected by autism. Data will be collected prospectively via clinical assessment, interviews, self-reports, medical record review, home environment assessments, and biologic samples that will be used in current analysis and stored for future studies. Planned analyses include a determination of whether in utero exposure to organic pollutants such as polychlorinated biphenyls (PCBs), brominated diphenyl ethers (BDEs), and persistent organic pollutants (POPs) is associated with autism risk.

→ For more information, see http://earlistudy.org
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIEHS**)

Population Research: Given the Nation's increasing diversity and changing demographics, it is critical to understand how trends in such areas as immigration, fertility, marriage patterns, and family formation affect the well-being of children and families. NIH research in these areas allows policymakers and program planners to better address public health needs. For instance:

- The Fragile Families and Child Well-Being Study follows children born to unmarried parents to assess how economic resources, father involvement, and parenting practices affect children's development.
- The New Immigrant Survey follows the first nationally representative sample of legal immigrants to the United States, providing accurate data on legal immigrants' employment, lifestyles, health, and schooling before and after entering the country.
- Several NIH Institutes are supporting The National Longitudinal Study of Adolescent Health, which integrates biomedical, behavioral, and social science data to discover the pathways that lead to health and/or disease in adulthood.

→ For more information, see http://www.cpc.unc.edu/addhealth/
→ For more information, see http://nis.princeton.edu/index.html
→ For more information, see http://www.fragilefamilies.princeton.edu/index.asp
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NICHD**, NCI, NCMHD, NIA, NIAAA, NIAID, NIDA, NIDCD, NINR, OAR, OBSSR, ORWH)

The Early Childhood Longitudinal Study (ECLS) program: The National Center for Education Statistics, within the Institute of Education Sciences of the U.S. Department of Education, is conducting an ongoing study of a nationally representative sample of children from diverse socioeconomic and racial/ethnic backgrounds who will start kindergarten in 2011. Several Federal agencies, including NIH, are partnering on the study to determine how a variety of home, school, community, and student factors influence the transition of children to school; frame their early school experiences; shape their later school experiences; relate to normal cognitive, social, emotional, and physical child development; and affect academic performance over time. NIH is participating in a field test to work out logistics to determine the feasibility of

adding a hearing and vision screening examination in the ECLS. ECLS is the only recent, nationally representative data collection program that enables statistical analysis of relationships between hearing and communication impairments or disorders and subsequent child development from infancy through eighth grade. The intent is to measure the hearing and vision of children during their first year of formal schooling, find out how hearing and vision change as a child grows, establish whether hearing and vision influence other aspects of normal child development, and clarify whether academic performance is influenced by hearing and vision. This information can be used then to evaluate how well early identification and intervention strategies were implemented during the birth cohort years from an earlier ECLS study.

→ For more information, see http://nces.ed.gov/ECLS/
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NEI, NIDCD**)

The National Children's Study (NCS): NCS promises to be one of the richest information resources available for answering questions related to children's health and development and will form the basis of child health guidance, interventions, and policy for generations to come. The landmark study will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. This extensive research effort will examine factors ranging from those in the natural and man-made environment to basic biological, genetic, social, and cultural influences. By studying children through their different phases of growth and development, researchers will be able to understand better the role of these factors in both health and disease. Specifically, the NCS will identify factors underlying conditions ranging from prematurity to developmental disabilities, asthma, autism, obesity and more. The study is led by a consortium of Federal agencies including NIH, CDC, and the EPA.

→ For more information, see http://www.nationalchildrensstudy.gov
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (I) (**NICHD**, NIEHS)

Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS): HANDLS is a community-based study to evaluate health disparities in socioeconomically diverse African American and white adults in Baltimore. Planned recruitment of 4,000 participants is more than three-quarters complete. Scientists are using mobile medical research vehicles to make possible onsite bone density and carotid artery imaging, physical examination and blood sampling, physical and cardiovascular performance, participant interviews, cognitive testing, and psychophysiological testing. HANDLS also will include studies of other variables, including: nutrition, environment and neighborhood effects, genetic make-up, family history, and access to health care. Participants will be followed over a 20-year period to allow researchers to gain insights into the physical, genetic, biologic, demographic, and psychosocial traits that may be most critical for healthy aging.

→ For more information, see http://handls.nih.gov
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIA**)

Rehabilitation

Neural Interfaces Program: Neural interfaces are systems that operate at the intersection of the nervous system and an internal or external device, including neural prosthetics. Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. NIH pioneered the development of this technology, beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants, which help people with hearing impairments; respiratory and

hand grasp devices for people with spinal cord injuries; and deep brain stimulation for Parkinson's disease, among other contributions. Current work aims to restore voluntary bowel and bladder control and standing to spinal cord-injured persons, allow paralyzed persons to control devices directly from their brains, improve cochlear implants, and improve deep brain stimulation, which may be applicable to many brain disorders. Through the years, the program has fostered the development of a robust research community, now including private sector companies, and represents a cooperative effort among several ICs, which also coordinate their efforts with programs that now are underway in the Department of Veterans Affairs and Department of Defense.

→ For more information, see http://www.ninds.nih.gov/funding/research/npp/index.htm
→ For more information, see http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*
→ (E) (**NINDS**, NEI, NIBIB, NICHD, NIDCD)

Traumatic Brain Injury Program: Traumatic brain injury (TBI) presents enormous challenges because TBI affects so many people and can compromise virtually any human ability, depending on which parts of the brain are damaged. NIH research ranges from how TBI causes immediate and delayed damage to brain cells, to development of markers of damage, through large clinical trials to test interventions. Multicenter clinical trials now are testing hypothermia (cooling) in children and use of the hormone progesterone to minimize damage in adults. In addition, NIH launched a program to collect data on the use of multidrug combinations to better treat traumatic brain injury. Because the high rate of TBI among military personnel in Afghanistan and Iraq presents a special concern, a Federal Interagency TBI Research group now coordinates among NIH, VA, DOD, and other agencies. Trans-agency workshops have focused on TBI classification (Oct. 2007), combination therapies for TBI (Feb. 2008), opportunities and challenges of blast injury-induced TBI (April 2008), and “Integrated Research on Psychological Health and TBI: Common Data Elements” (March 2009). NIH is working with CDC on how to better track TBI in former military personnel and on evaluating the effectiveness of rehabilitation for TBI. The NINDS intramural research program has worked with the VA and DOD for many years on long-term neuropsychological outcomes of TBI in Vietnam veterans, and now in Iraq veterans. The NIH Intramural Research Program also is partnering now with the Uniformed Health Services University of the Health Sciences Center in the joint Center for Neuroscience and Regenerative Medicine, whose extensive TBI research programs range from molecular studies to understanding TBI mechanisms through rehabilitation and outcomes research.

→ For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Neurological_Effects_of_Blast_Injury_Workshop.htm
→ For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Combination_Therapies_for_Traumatic_Brain_Injury_Workshop.htm
→ For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Classification_of_Traumatic_Brain_Injury_Workshop.htm
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-003.html
→ For more information, see http://www.usuhs.mil/cnrm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E, E/I) (**NINDS**, CC, NICHD, NIMH, NINR)

Prostheses to Restore Lost Function: Many veterans return home with significant injuries to their extremities, including loss of limbs. Through multidisciplinary partnerships between engineers, clinicians, scientists, and industrial partners, NIH investigators are developing new and novel technology for assistive rehabilitation, such as electrodes for neural and muscular recordings, networked implantable systems for functional electrical stimulation, robotics for rehabilitation, and brain computer interface systems for communication and control. For example, next-generation hand and arm prosthesis systems controlled by intact muscle recordings will be able to produce fine finger movements and provide to the user the

sensation of position and force applied to an artificial hand. Other examples include multifunctional stimulation systems that allow spinal cord-injured subjects to change posture, stand, step, and control hand and arm function.

→ Weir RF, et al. *IEEE Trans Biomed Eng* 2009;56(1):159-71. PMID: 19224729.
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIBIB**)

Center for Neuroscience and Regenerative Medicine: The Center for Neuroscience and Regenerative Medicine (CNRM) is a collaborative initiative between NIH and the U.S. Department of Defense (DOD). The center's research mission is to discover methods to better intervene and prevent the long-term consequences resulting from traumatic brain injury (TBI). To increase research capabilities, the United States Congress established the CNRM as a collaborative intramural program and appropriated funds to the DOD for implementation. CNRM will study combat casualties cared for at Walter Reed Army Medical Center (WRAMC) and the National Naval Medical Center (NNMC) using advanced molecular and neuroimaging technology at the NIH CC. The CNRM seeks to serve as the catalyst for collaboration, innovation, and advancement of knowledge of the incidence of TBI and the identification of interdisciplinary approaches to assess TBI and promote recovery. CNRM research programs address the full spectrum of TBI, including the effect of high anxiety and the concurrent development of post-traumatic stress disorder with TBI. In addition, the center will evaluate civilian patients with brain injury following trauma, to understand the relationship between military and civilian brain injury in patients as well as in preclinical models. CNRM research programs focus on (a) diagnostics and imaging, (b) biomarkers, (c) neuroprotection and models, (d) neuroregeneration, (e) neuroplasticity, and (f) rehabilitation and evaluation. The program leverages the strengths of NIH in neurosciences and neuroimaging together with DOD experience in brain trauma, neuroregeneration, and modeling.

→ For more information, see http://www.usuhs.mil/cnrm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (I) (**CC, NINR**, NIMH, NINDS)

Advancing Research on Prosthetics: NIH is investing strategically to develop improved prosthetic devices that can help soldiers and other individuals who have lost limbs or who have suffered a traumatic injury resume normal activities. Earlier research in movement control paved the way for a new nerve-muscle graft procedure that enables amputees to have more natural control of a prosthetic device. NIH now is stimulating the development of advanced methods to eliminate infection when lower limb prostheses are directly attached to bones. And, through Small Business Innovation Research Awards, NIH continues to support research to develop cutting edge sensors for prosthetic devices and virtual reality systems to enhance rehabilitation. In response to the rise in the number of individuals who need prosthetic and orthotic devices, NIH also is encouraging research on the development of outcome measures to help assess the effectiveness of those devices. This research ultimately will provide clinicians the information they need to optimize rehabilitation and quality of life for amputees and an aging population.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-012.html
→ (E) (**NICHD**)

Laryngeal Tissue Regeneration: The vocal folds (also referred to as vocal cords) are two elastic bands of muscle tissue located in the larynx (voice box) directly above the trachea (windpipe). The vocal folds produce voice when air held in the lungs is released and passed through the closed vocal folds, causing them to vibrate. Vocal fold scars can result from injury or inflammation, or as a consequence of surgery to remove vocal fold nodules or polyps. The scars increase vocal fold stiffness and reduce their ability to vibrate. An individual with scarred vocal folds may have a hoarse, breathy, or low-pitched voice. NIH-supported scientists have developed a new class of soft gel material to serve as a scaffold to encourage regeneration of vocal fold tissue. Specific particles within the material also can be modified to bind and slowly release

therapeutic drugs within the vocal folds as a way to further encourage regeneration of the native tissue. Scientists now are testing this new material to learn more about what types of changes (to particle size, distribution, etc.) will optimize tissue regeneration. Once the gel is optimized in laboratory tests, it will offer the hope of treatment for individuals whose vocal folds have been damaged due to scarring.

→ Jha A, et al. Structural Analysis and Mechanical Characterization of Hyaluronic Acid-Based Doubly Cross-Linked Networks. *Macromolecules* 2009;42:537-46.
→ For more information, see http://www.nidcd.nih.gov/health/voice/takingcare.htm
→ For more information, see http://pubs.acs.org/doi/abs/10.1021/ma8019442
→ (E) (**NIDCD**)

Stem Cells and Regenerative Medicine: Stem cells are able to renew themselves and generate progeny that differentiate into more specialized cells. They play critical roles in organism development, and some are essential for normal homeostasis and tissue repair. NIH has made a significant investment in stem cell research. One NIH-supported study showed that the sex of cells in a subpopulation of muscle-generating stem cells in adult mice can influence their capacity to repair tissue considerably. This finding could lead to future therapies for various diseases, including muscular dystrophy. A collaboration between NIH Intramural researchers and those at Walter Reed Army Medical Center discovered that waste tissues from surgery, removed to promote healing of orthopaedic injuries and war-traumatized muscle, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells. They could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest cells. NIH has partnered with the Department of Defense on an initiative to speed treatments to wounded soldiers abroad, and civilian trauma victims and burn patients in the United States. This collaboration has resulted in the establishment of the new Armed Forces Institute of Regenerative Medicine (AFIRM). The AFIRM-led program will focus on regrowing fingers, repairing shattered bones, and restoring skin to burn victims with genetically matched skin, to pave the way for commercial products in the near future. Hair follicles are useful models for organ regeneration. Recent discoveries have been made in the molecular processes that govern the growth of hair follicle stem cells, which are a source for newly formed hair follicles.

→ Deasy BM, et al. *J Cell Biol* 2007 Apr 9;177(1):73-86. PMID: 17420291. PMCID: PMC2064113.
Jackson WM, et al. *J Tissue Eng Regen Med* 2009 Feb;3(2):129-38. PMID: 19170141.
Plikus MV, et al. *Nature* PMID: 18202659. PMCID: PMC2696201.
Horsley V, et al. *Cell* 2008 Jan 25;132(2):299-310. PMID: 18243104. PMCID: PMC2546702.
Nesti LJ, et al. *J Bone Joint Surg Am* 2008;90(11):2390-8. PMID: 18978407. PMCID: PMC2657299.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cell_sex_and_stem_cell.asp
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/progenitor_cells.asp
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*, Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
→ (E/I) (**NIAMS**, NIA, NIAID, NIBIB)

Bioactive Nanostructures for Neural Regeneration: Spinal cord injury (SCI) often leads to permanent paralysis and loss of sensation below the site of injury because of the inability of damaged axons to regrow across the injury site in adults. Nanomaterials built from a family of self-assembling molecules may offer hope for treating serious injuries, such as spinal cord injury according to new results from NIH research. Recently, an NIH-supported research group developed peptide amphiphile (PA) molecules that self-assemble in vivo into supramolecular nanofibers and tested them on mouse models of spinal cord injury. In this work, in vivo treatment with the PA nanofibers, after SCI, reduced cell death and promoted regeneration of both motor fibers and sensory fibers through the lesion site. Treatment with the PA also resulted in significant behavioral improvement. These observations demonstrate that it is possible to inhibit glial scar formation and to facilitate regeneration after SCI using bioactive three-dimensional nanostructures displaying high densities of neuroactive epitopes on their surfaces.

→ Tysseling-Mattiace VM, et al. *J Neurosci* 2008;28(14):3814-23. PMID: 18385339. PMCID: PMC2752951.
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*
→ (E) (**NIBIB**)

Other Notable Examples

Clinical Research Networks: Clinical research is essential for translating laboratory findings into evidence-based interventions targeting an array of public health concerns. Many research programs involve collaborative networks, drawing scientists together to bring the benefits of clinical research to high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. Among such networks that have generated significant findings to advance medical practice and improve public health are the Maternal and Fetal Medicine Network, Neonatal Research Network, Obstetric Pharmacology Research Network, Pediatric Critical Care Research Network, Pelvic Floor Disorders Network, Traumatic Brain Injury Clinical Trials Network, and Global Network for Women's and Children's Health Research.

→ For more information, see http://www.bsc.gwu.edu/mfmu/index.html
→ For more information, see https://neonatal.rti.org
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-002.html
→ For more information, see http://www.cpccrn.org
→ For more information, see http://www.pfdnetwork.org
→ For more information, see http://www.tbi-ct.org/
→ For more information, see http://gn.rti.org/about/index.cfm
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NICHD**, FIC, NCCAM, NCI, NIDCR, ORWH)

Addressing Drug Abuse and Comorbidities in Returning Vets and Their Families: Sustained U.S. combat operations in Afghanistan and Iraq have resulted in military personnel experiencing increased numbers and lengths of deployments and greater exposure to traumatic stressors. Stress can be a major contributor to both the onset and exacerbation of substance abuse and other mental health problems, and can lead to relapse in former substance abusers. To understand better the intervention needs of this group, NIH in 2009 sponsored a 2-day meeting to formulate a research agenda for conducting addiction prevention and treatment research with military and veteran populations and their families. Collaborators included the U.S. Army Medical Research and Materiel Command, the Department of Defense Health Affairs, the Army Center for Substance Abuse Programs, the Department of Veterans Affairs, and several NIH ICs. Subsequently, a call for studies on trauma, stress, and substance use and abuse among U.S. military personnel, veterans, and their families was issued. It focuses on epidemiology/etiology, screening and identification, and prevention and treatment of substance use and abuse—including alcohol, tobacco, and other drugs—and associated problems (e.g., PTSD, traumatic brain injury, sleep disturbances, and relationship violence) among U.S. military personnel, veterans, and their families. Further, NIH's National Drug Abuse Treatment Clinical Trials Network (CTN) is developing a protocol concept for the treatment of PTSD and drug abuse/dependence in veteran populations. It is expected that this study will be conducted in clinics participating in the CTN, which include some Veterans Administration hospitals and research facilities.

→ For more information, see http://www.drugabuse.gov/pdf/tib/veterans.pdf
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIDA**, NCI, NIAAA, NIMH)

Transdisciplinary Tobacco Use Research Centers—Alcohol Use and Smoking: Multiple Institutes at NIH are co-funding seven collaborative, transdisciplinary centers to identify familial, early childhood, and lifetime psychosocial pathways related to smoking initiation, use, cessation, and patterns of dependence. Research on genetics of addiction, physiological biomarkers, and the use of advanced imaging techniques can lead to individualized and community approaches for tobacco prevention and treatment. This model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships. Some recent highlights include: For smokers quitting while taking the prescription drug bupropion, the risk of smoking relapse was associated primarily with heavy, rather than with moderate drinking. Interactions between brain pathways activated by nicotine and alcohol may increase the likelihood of drinking in humans who simultaneously smoke and drink, suggesting that drugs that block nicotinic receptors also may help to reduce drinking. Varenicline, an agonist of certain nicotinic acetylcholine receptors, is a smoking cessation medication that has been shown in preclinical research to reduce alcohol drinking. Researchers are testing varenicline in preclinical models of ethanol drinking to determine which nicotinic receptor subtypes are most important. Recently, they found that varenicline reduces alcohol self-administration in heavy-drinking smokers.

→ For more information, see http://dccps.nci.nih.gov/tcrb/tturc
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIAAA**, NCI, NIDA)

Testing for Reproductive Tumors in the National Toxicology Program's Carcinogenesis Bioassay: Perinatal Dosing: The National Toxicology Program (NTP) evaluates substances for a variety of health-related effects. Two-year studies in laboratory rodents remain the primary method by which chemicals or physical agents are identified as having the potential to be hazardous to humans. In 2006, NTP convened a workshop on Hormonally Induced Reproductive Tumors, Relevance of Rodent Bioassays to discuss the adequacy of rodent models used in the 2-year bioassay for detecting reproductive tumors. The workshop recommended that in utero and lactational exposures could be added to the chronic bioassay depending upon what is known about the mode of action. For detecting tumor types such as testicular germ cell tumors, this recommendation was especially strong. In utero and lactational exposures should be considered for mammary tumor studies if there are any developmental effects associated with a substance under study that involved endocrine tissues, steroid receptor binding, a change in mammary gland morphology, or altered timing of vaginal opening. NTP has conducted such perinatal exposures on cancer bioassays in the past, but only when there was special justification for such a design to be adopted. A new default design in which dosing will start in pregnancy and be continued throughout life or to the end of a 2-year period now has been adopted unless there is a good scientific reason not to undertake such a study. NTP has initiated studies to obtain data for constructing physiologically based pharmacokinetic (PBPK) models in rodents and nonhuman primates. It is planning studies to explore the long-term consequences of perinatal exposure to Bisphenol A to understand the potential impact to humans of the developmental changes reported in numerous laboratory animal studies. It is hoped that the PBPK models will link information from rodent studies with primate studies, and potentially with human outcomes.

→ This example also appears in Chapter 2: *Cancer*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (O) (**NIEHS**)

Bisphenol A Exposure and Effects: More than 90 percent of the U.S. population is exposed to low levels of BPA. Exposures may occur through use of polycarbonate drinking bottles and the resins used to line food cans. The NIH National Toxicology Program's (NTP's) Center for the Evaluation of Risks to Human Reproduction conducted an evaluation to determine whether current levels of exposure to BPA present a hazard for human reproduction and/or development. Following this evaluation of existing literature, the NTP expressed “some concern” for effects on the brain, behavior, and prostate gland based on developmental effects reported in some laboratory animal studies using BPA

exposures similar to those experienced by humans. NIH is working to address and support research and testing needs identified during the NTP evaluation to understand any potential risks for humans from BPA exposure. In collaboration with scientists at the FDA National Center for Toxicological Research, the NTP has designed and begun studies to evaluate similarities and differences in how rats metabolize BPA in relation to nonhuman primates, and to further understand the long-term health consequences from exposures to low levels of BPA during rodent development. In addition, NIH is providing grant support to the extramural community for studies that focus on investigating possible long-term health outcomes from developmental exposure or chronic exposures to environmentally relevant doses of BPA. Collectively, these studies should address research gaps, reduce uncertainties, and provide perspective regarding any potential risk that BPA poses for public health.

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→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*

→ (I) (**NIEHS**)

NIH Strategic Plans Pertaining to Life Stages, Human Development, and Rehabilitation Research

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

- *Demographic and Behavioral Sciences Branch Goals and Opportunities, 2002-2006*
- *Pregnancy and Perinatology Branch Strategic Plan, 2005-2010, 2003*
- Surgeon General's Conference on the Prevention of Preterm Birth
- Closing the Gap: A National Blueprint to Improve the Health of Persons with Mental Retardation
- Child and Adolescent Development Research and Teacher Education: Evidence-based Pedagogy, Policy, and Practice
- Workshop to Develop an Agenda on Research Settings for Rehabilitation

Branch Reports to Council with Future Scientific Directions:

- *Mental Retardation and Developmental Disabilities (MRDD) Branch, Report to the NACHHD Council, June 2005*
- Division of Epidemiology, Statistics, and Prevention Research (DESPR), NICHD, Report to the NACHHD Council, September 2005
- *National Center for Medical Rehabilitation Research (NCMRR) Report to the NACHHD Council, January 2006*
- *Developmental Biology, Genetics and Teratology Branch Report to the NACHHD Council, September 2006*
- *Reproductive Sciences Branch, NICHD Report to the NACHHD Council, January 2007*

- *Pediatric, Adolescent, and Maternal AIDS Branch (PAMAB), NICHD, Report to the NACHHD Council, June 2007*
- *Demographic and Behavioral Sciences, NICHD Report to the NACHHD Council, September 2007*
  - *Demographic and Behavioral Sciences (DBS) Branch Long-Range Planning 2006-2007: Highlights from a Panel Discussion*
- Obstetric and Pediatric Pharmacology Branch (OPPB), NICHD, Report to the NACHHD Council, January 2008
- Contraception and Reproductive Health Branch (CRHB), NICHD, Report to the NACHHD Council, June 2008
- Pregnancy and Perinatology Branch (PPB), NICHD, Report to the NACHHD Council, September 2008
- Child Development and Behavior Branch (CDBB), NICHD, Report to the NACHHD Council, January 2009
- Endocrinology, Nutrition, and Growth (ENG) Branch Report to Council
- Intellectual and Developmental Disabilities (IDD) Branch Report to Council

National Cancer Institute (NCI)

- *NCI Strategic Plan for Leading the Nation*

National Eye Institute (NEI)

- National Eye Institute Strategic Planning
- *National Plan for Eye and Vision Research (2004)*
- *Progress in Eye and Vision Research 1999-2006*
- Ocular Epidemiology Strategic Planning Panel Report—Epidemiological Research: From Populations Through Interventions to Translation (2007)
- *Age-Related Macular Degeneration Phenotype Consensus Meeting Report*
- *Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration Workshop Report*
- *Report of the Advances in Optical Imaging Symposium*

National Institute of Dental and Craniofacial Research (NIDCR)

- *NIDCR Strategic Plan*
- *NIDCR Implementation Plan*

National Institute on Aging (NIA)

- *Living Long and Well in the 21st Century: Strategic Directions for Research on Aging*

National Institute on Drug Abuse (NIDA)

- *NIDA Five-Year Strategic Plan 2009*

National Institute on Deafness and Other Communication Disorders (NIDCD)

- *NIDCD Action Plan on Research Careers for Deaf Individuals*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- *National Institute on Alcohol Abuse and Alcoholism Five-Year Strategic Plan FY08-13*

Recommendations of the NIAAA Extramural Advisory Board (EAB)

- *Fetal Alcohol Spectrum Disorders Research*
- *Mechanisms of Behavioral Change*

National Institute of Nursing Research (NINR)

- *NINR Strategic Plan: Changing Practice, Changing Lives*

Office of Dietary Supplements (ODS)

- *Promoting Quality Science in Dietary Supplement Research, Education, and Communication: A Strategic Plan for the Office of Dietary Supplements, 2004-2009*

Trans-NIH Strategic Plans

- *NIH Research Plan on Down Syndrome*
  (**NICHD**, NCI, NHLBI, NIA, NIAID, NIDA, NIDCD, NIDCR, NIMH, NINDS)
- *NIH Research Plan on Fragile X Syndrome and Associated Disorders*
  (**NICHD**, NIMH, NINDS, NIA, NIDDK, NIGMS, NCI, NIDCD)
- *NIDDK Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*
  (CC, CSR, NCCAM, NCI, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, **NIDDK**, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)
- *NIH Action Plan for Transplantation Research (2007)*
  (NCI, NHLBI, NIA, NIAAA, **NIAID**, NIAMS, NIBIB, NIDA, NIDCR, NIDDK, NIMH, NINDS)

Interagency Plans

- 2009 Strategic Plan for Autism Spectrum Disorder Research
  (**NIH** [**NIMH**, NICHD, NIEHS, NIDCD, NINDS])**,** *ACF, CMS, CDC, HRSA, SAMHSA, HHS Office on Disability, U.S. Department of Education)*

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Minority Health and Health Disparities

In 1985, Secretary of Health and Human Services Margaret M. Heckler issued the Report of the Secretary's Task Force on Black and Minority Health*. This landmark report revealed the disproportionate burden of disease, disability, and death experienced by African Americans, Hispanics, Native Americans, and Asian/Pacific Islanders in the United States. In calling attention to this national crisis, Secretary Heckler elevated the elimination of health disparities to an important national priority and validated earlier concerns expressed in the Healthy People 1979 report. By 1990, the Office of Minority Programs was created administratively within the Office of the Director, NIH. Congressional legislation followed in 1993 that established the Office of Research on Minority Health (ORMH) and charged it with improving the health of vulnerable populations. With a small budget and no grant-making authority, ORMH partnered with a select group of NIH ICs to support vital programs focused on basic research, health education, and infrastructure development. A broadened and ambitious agenda for the field has been advanced since FY 2000 when Congress established the National Center on Minority Health and Health Disparities (NCMHD).*

Much has been accomplished over the years. Scientists are beginning to understand the genetic underpinnings of certain diseases such as systemic lupus erythematosus (lupus) and chronic kidney disease. NIH health education campaigns currently are improving the health literacy of vulnerable communities in critical areas such as cardiovascular disease and stroke, diabetes, cancer, HIV/AIDS, diseases of the eye, lupus, and Alzheimer's disease. Comprehensive Sickle Cell Centers are supporting multidisciplinary programs of basic, applied, and clinical research and also are providing patient services in diagnosis, counseling, and education concerning sickle cell disease and related disorders.

By mid-century, the U.S. Census Bureau projects that the Nation will be more racially and ethnically diverse. Racial/ethnic minorities, now roughly one-third of the U.S. population, are expected to become the majority population in 2042 and 54 percent of the U.S. population by 2050.[156,157] As the diversity of the U.S. population and the burden of diseases continue to increase, biomedical research to understand, predict, prevent, and treat diseases disproportionally burdening vulnerable populations is critical. NIH is at the forefront of confronting this challenge.

Introduction

Scientific and technological discoveries throughout the 20th century have improved the overall health of the Nation and generated hope for happier, healthier, and longer lives for all. However, some segments of the U.S. population continue to experience elevated morbidity and mortality, disproportionate incidence of disease and disability, and adverse outcomes in cancer, cardiovascular disease, diabetes, HIV/AIDS, infant mortality, and certain other conditions. These disparities in health are most visible in racial/ethnic minority groups, in individuals from socioeconomically disadvantaged backgrounds, and in people living in medically underserved areas including rural communities.

NIH has devoted considerable resources to characterizing the root causes of health disparities. As a result of these efforts, a complex and multifactorial web of interconnected and overlapping factors (i.e., biological, behavioral, environmental, and societal) has begun to emerge. For example, poverty and lack of education correlate with poor health and lower life expectancy; moreover, discrimination based on racial, ethnic, and linguistic differences in the United States not only triggers biological stress, but also creates a barrier to accessing high-quality health care. In addition, some groups are genetically susceptible to certain diseases, and when this inherited biological vulnerability combines with adverse social and/or environmental factors (e.g., poor diet, pollution, economic stress), these groups exhibit poorer health outcomes. These are some of the interrelated factors that contribute to the existence of health disparities. Confronting this formidable challenge is at the heart of the vigorous efforts NIH is undertaking to make advances in science that will translate into effective prevention and treatment interventions.

In keeping with its role as the Nation's steward of biomedical and behavioral research, NIH is firmly committed to ultimately eliminating health disparities in the United States. Since the issuance of the *Black and Minority Health Report* in 1985, NIH has incorporated the goals of improved health for all Americans and the elimination of health disparities in its support of biomedical and behavioral research, research training, research capacity-building, outreach, and research and health information dissemination. Many of these activities are multidisciplinary collaborations involving several NIH ICs or NIH and non-Federal organizations. These efforts not only have advanced health disparities research, but also have facilitated communications among stakeholders and moved the field forward exponentially during the last 24 years.

NIH programs to address minority health and health disparities are guided by the *NIH Health Disparities Strategic Plan and Budget*. NIH conducts and supports research, training, dissemination of information, and other programs that address the health conditions of racial/ethnic minorities and other populations experiencing health disparities. This comprehensive document, which sets the overarching principles for the NIH health disparities agenda, focuses on three major goals: (1) to conduct and support intensive research on the pathophysiological, epidemiological, and societal factors underlying health disparities; (2) to expand and enhance research capacity to create a culturally sensitive and culturally competent workforce; and (3) to engage in aggressive, proactive community outreach, information dissemination, and public health education. All NIH ICs have a minority health and health disparities strategic plan, and those efforts are captured within this plan.

In December 2008, NIH convened the first trans-NIH health disparities summit to showcase the collective investment, contributions, and partnerships in health disparities research among NIH ICs and other Federal government agencies, and within the private sector. This 3-day forum, *The NIH Science of Eliminating Health Disparities Summit*, was structured into 3 multitopic plenary sessions and 5 distinct breakout session tracks consisting of both oral and poster presentations of pioneering health disparities research. The third day closed with a town hall meeting. More than 4,000 researchers, scientists (including those in the social, behavioral, environmental, and political sciences), public health professionals, community leaders, health advocates, and stakeholders with an interest in health disparities attended to (a) assess current advances in health disparities research and interventions, (b) examine gaps in research and data, (c) explore conceptual frameworks and theories, and (d) provide recommendations to NIH for advancing health disparities research through the translation of science into practice and effective policy.

In 2008, more than 4,000 scientists, public health professionals, community leaders, health advocates, and stakeholders with an interest in health disparities gathered to assess current advances in health disparities research and interventions, examine gaps in research and data, explore conceptual frameworks and theories, and provide recommendations to NIH for advancing health disparities research. The recommendations that emerged from this conference will help to continue shaping the NIH health disparities research agenda and specifically inform the next iteration of the NIH Health Disparities Strategic Plan FYs 2009-2013.

A *Science, Policy, and Practice* framework for addressing health disparities was proposed as an overarching, organizational construct to promote advances to identify ways to bridge science, practice, and policy and to shape future research. Researchers focused attention on the links between biological and nonbiological determinants of health in health disparity populations. Participants particularly stressed (1) the critical need for health and health care reform; (2) the adoption of a life-course approach to addressing disparities and the social determinants of health; (3) the integration of eliminating health disparities as a goal not only within public health policies, but also within social, environmental, educational, and institutional policies that are known to have a direct impact on health; and (4) the need for partnerships, collaborations, and community engagement in health disparities research.

The summit set some broad goals for the next decade for the NIH health disparities research agenda: (1) enhance trans-NIH collaborations in health disparities research and develop stronger Federal collaborations that will advance both science and research while providing effective methods to measure outcomes; (2) adopt a research framework at the intersection of science, practice, and policy that includes the biological and nonbiological determinants of health;

(3) embrace a research process that recognizes and acknowledges the unique strengths of partnerships, collaborations, community engagement, and transdisciplinary efforts; (4) promote outreach in the news media; and (5) continue to support capacity-building and infrastructure development to nurture a research training pipeline that produces a highly motivated, diverse workforce of researchers dedicated to eliminating our Nation's most critical health disparities. These recommendations will inform the next version of the *NIH Health Disparities Strategic Plan for FYs 2009-2013.*

Burden of Illness and Related Health Statistics

Health disparities affecting racial/ethnic minorities and other medically underserved populations are seen across a broad spectrum of diseases and conditions. They represent one of the most persistent public health challenges in the United States.

Health disparities affecting racial/ethnic minorities and other medically underserved populations are seen across a broad spectrum of diseases and conditions. They represent one of the most persistent public health challenges in the United States. Research findings consistently have shown that many health disparity populations also are less likely than most of the majority population to receive needed health care services, including clinically necessary procedures. Health disparities frequently are associated with differences in socioeconomic status (SES) and tend to diminish significantly and, in a few cases, disappear when SES factors are controlled. Nevertheless, some racial/ethnic disparities remain even after adjusting for SES differences and other factors related to health care access.[158] For details on the depth and breadth of this burden, see the following table of data, presented by disease and condition.

About Various Health Disparities Affecting Racial and Ethnic Minorities and Other Medically Underserved Populations in the United States

Cancer: The variation in cancer burden among various medically underserved, racial/ethnic minority, and low-income populations indicates statistically significant disparities between populations and within subpopulations. For example, African Americans are more likely to develop and die from cancer than any other racial/ethnic group. The cancer death rate for African American males and African American females is 36 percent and 17 percent higher than among white males and white females, respectively. The 5-year survival rate for all cancers combined is lower for African Americans (58 percent) than for whites (68 percent). Hispanics, Asian Americans, and Pacific Islanders have a lower incidence for some common cancers, but have appreciably higher rates of cancers associated with infection, such as uterine, cervical, liver, and stomach cancer. For Asian American subpopulations, cervical cancer among Vietnamese women is three times higher than among Chinese and Japanese women. Mortality rates for renal cancer in American Indians and Alaska Native men and women are higher than in any other racial/ethnic population.[159] Cancer patients with low SES have more advanced cancers at diagnosis, receive less aggressive treatment, and have higher risk of dying in the 5 years following cancer diagnosis.[160] Women who lack health insurance have the lowest rates of mammography screening (24 percent). Similarly, there is persistent underuse of the Pap test among women who are uninsured, recent immigrants, and those with low education.[161]

Coronary Heart Disease and Stroke: Despite remarkable reductions in cardiovascular morbidity and mortality during the past 4 decades, some racial/ethnic minorities still bear a disproportionate share of the burden. Rates of heart disease have been consistently higher for the African American population than for whites. In 2005, coronary heart disease age-adjusted death rates for African American men (329.8 per 100,000) and African American women (228.3 per 100,000) were 28 and 36 percent higher than for white men and women, respectively.[162] In the period 2003-2006, stroke affected 3.3 percent of the African American population under 75 years of age, compared to 2 percent of whites under age 75.[163] Age-adjusted death rates for stroke were 46 percent higher in the black/African American population than the white population.[164] Death certificate data from 2002 show that mean age at stroke death was younger among African

Americans, American Indians/Alaska Natives, and Asians/Pacific Islanders than among whites. The mean age at stroke death also was younger among Hispanics than non-Hispanics.[165]

HIV/AIDS: In 2007, blacks comprised approximately 13 percent of the U.S. population, but accounted for 48 percent of all persons living with HIV/AIDS in the 34 states with long-term, confidential, name-based HIV reporting. In 2007, HIV/AIDS rates (per 100,000 population) were 76.7 among black/African Americans, 34.6 among Native Hawaiian/Other Pacific Islanders, 27.7 among Hispanics, 12.8 among American Indians/Alaska Natives, 9.2 among whites, and 7.7 among Asians.[166] Certain subpopulations are disproportionately affected. Among females—for whom the predominant transmission category was high-risk heterosexual contact—the HIV incidence rate for black/African Americans is 14.7 times that of whites, and for Hispanics it was 3.8 times the rate.[167] In general, blacks/African Americans, especially black/African American males, and men having sex with men (of all races) were represented disproportionately in 2006 among persons with new HIV infection.[168] In 2004, Puerto Rico was among the top 10 U.S. states and territories with the highest number of AIDS cases, with an estimated 10,000 persons living with AIDS. The rate for adults and adolescents in Puerto Rico with AIDS was estimated to be 324 per 100,000 population.[169]

Infant Mortality: While the overall infant mortality rate decreased 2.6 percent between 2005 and 2006, a disparity in infant mortality rates between black/African Americans (13.3 deaths per 1,000 live births) and whites (5.6 deaths per 1,000 live births) remained.[170] For Hispanic Americans, the infant mortality rate varies among subpopulations. In 2005, the rate for Cubans was 4.4 per 1,000 live births, while the rate for Puerto Ricans was 8.3 per 1,000 live births. Puerto Ricans have a 40 percent higher infant mortality than that of non-Hispanic whites.[171] Rates of premature birth also are higher for racial/ethnic minority groups. Preliminary data for 2007 show that 18.3 percent of non-Hispanic black newborns and 13.9 percent of American Indian newborns were born preterm compared to 11.5 percent of non-Hispanic white newborns and 10.9 percent of Asian or Pacific Islander newborns. For non-Hispanic blacks, there also is a higher percentage of low-birth-weight babies. Preliminary 2007 data show that 13.8 percent of non-Hispanic black babies were born at low birth weight, compared with 7.2 percent of non-Hispanic white babies.[172]

Type 2 Diabetes: According to 2004-2006 national survey data, racial/ethnic disparities in type 2 diabetes exist for persons ages 20 years or older. American Indian/Alaska Natives and black/African Americans are affected disproportionately. During that timeframe, 15 percent of the American Indian/Alaska Native population[173] and 11.8 percent of the non-Hispanic black/African American population were diagnosed with diabetes compared to 6.6 percent of non-Hispanic whites, 7.5 percent of Asian Americans, and 10.4 percent of Hispanics.[174] The rate of diabetes is particularly striking among the Pima Indians. One in 2 adult Pima Indians has diabetes, and among those with diabetes, 95 percent are overweight.[175] Among Hispanics, there is marked heterogeneity in diabetes rates for the different Hispanic subgroups, namely, 8.2 percent for Cubans, 11.9 percent for Mexican Americans, and 12.6 percent for Puerto Ricans.[176] Hispanics also experience complications of diabetes disproportionately. Hispanics of all races experienced more age-adjusted years of potential life lost before age 75 per 100,000 population than non-Hispanic whites for diabetes (41 percent more) and other causes of death such as stroke (18 percent more) in 2001.[177] In 2005, Hispanics were 1.6 times as likely to die from diabetes as non-Hispanic whites, and also had higher rates of obesity and hypertension.[178] Similar to the occurrence in adults, African American, Native American, and Hispanic children and adolescents are disproportionately afflicted with type 2 diabetes.[179]

Asthma: The prevalence of asthma among non-Hispanic blacks was approximately 30 percent higher than among non-Hispanic whites and approximately double that of Hispanics in 2002.[180] According to data on U.S. children from the 2007 National Health Interview Survey, non-Hispanic black children, poor children, and children who were reported to be in poor health, had higher prevalence of asthma. Specifically, non-Hispanic black children were more likely to have ever been diagnosed with asthma (20 percent ever diagnosed) than Hispanic (13 percent) or non-Hispanic white children (11 percent). Asthma was more likely to be diagnosed in children from poor families (17 percent) than in children from non-poor families (12 percent), and in children in poor health (41 percent) than in children in excellent or very good health (11

percent).[181] In 2005, for Hispanic subpopulations, specifically Puerto Ricans, the asthma prevalence rate was 125 percent higher than that of non-Hispanic whites and 80 percent higher than non-Hispanic blacks. Moreover, Puerto Ricans had the highest rate of asthma attacks in the prior year, which was 140 percent higher than that of non-Hispanic whites. American Indians and Alaska Natives had a 40 percent higher rate than non-Hispanic whites.[182]

Mental Illness: Disease burden associated with mental disorders also varies across racial/ethnic minority populations. Native Americans and Alaska Natives, for example, not only have disproportionately higher rates of depression, but also experience higher rates of suicide than do other populations.[183] Suicide rates among American Indian/Alaskan Native adolescents and young adults aged 15 to 34 (21.7 per 100,000) are 2.2 times higher than the national average for that age group.[184] Although African Americans are less likely than whites to experience a major depressive disorder, when they do, it tends to be more severe and lasts nearly 50 percent longer.[185] Young African Americans—specifically those between the ages of 10 and 14—experienced a dramatic increase in suicide rates between 1980 and 1995; the rate increased 233 percent vs. 120 percent for their non-Hispanic white counterparts. Moreover, African Americans are overrepresented in populations at high risk for mental illness, including homeless and incarcerated populations, children in foster care and the child welfare system, and persons exposed to violence.[186] Differences also exist within racial/ethnic minority populations. Second- or later-generation Caribbean black, Latino, and Asian immigrants have been found to have higher rates of mental disorders than do first-generation immigrants.[187] These findings also vary across subgroups.[188]

Eye Diseases: Disparities in eye diseases are experienced among racial/ethnic minorities. Glaucoma is a blinding visual disorder resulting from damage to the optic nerve. In 2000, approximately 2.2 million people ages 40 years or older were estimated to have the most common form of glaucoma, and it is projected that by 2020, this will grow to 3.4 million. Glaucoma is the leading cause of irreversible blindness in African Americans and Hispanics, and is almost three times more common in African Americans compared to whites. Among Hispanics, the prevalence of glaucoma is seen to rise rapidly after age 65.[189,190]

Dental Caries, Oral and Pharyngeal Cancer, and Periodontal Diseases: The U.S. Surgeon General's Report: Oral Health in America[191] and recent epidemiologic studies document that underserved and racial/ethnic minority populations experience disproportionate burdens of dental caries, oral and pharyngeal cancer, and periodontal diseases.[192,193] Dental caries, an infectious disease that affects quality of life, is one of the most prevalent health conditions in the United States. The distribution of dental caries in primary teeth by race/ethnicity is uneven, with 55 percent of Mexican American and 43 percent of African American children ages 2 to 11 experiencing this disease compared with 39 percent of whites, according to the National Health and Nutrition Examination Survey (NHANES), 1999-2004. Comparable differences are seen between poor and more affluent children (54 percent vs. 32 percent, respectively). Among poor children, more than half of this decay is untreated.[194]

The American Cancer Society recently estimated that approximately 31,000 new cases and 7,320 deaths per year were attributable to oral cavity and pharyngeal cancer. The prognosis of these cancers is poor, especially when they are detected at a late stage. Black/African American males and subgroups of Hispanic male populations are known to be at increased risk for late-stage malignancies that are less amenable to treatment and have poorer survival rates. For white males the 5-year survival rate for oropharyngeal cancer is 61 percent compared to 38 percent for black/African American males.[195]

Health disparity populations are more likely to experience periodontal disease, which range from mild forms of gingivitis to severe forms of periodontitis. For example, black/African Americans are more likely than whites to have periodontitis. Similar levels of inequalities in periodontal disease also exist by education level and poverty level.[196]

Systemic Lupus Eythematosus (Lupus): Lupus is a serious and potentially fatal autoimmune disease, often occurring in women of child-bearing age. It can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. People of all races can have lupus, but incidence in African American women is three times higher than

in white women.[197] They tend to develop the disease at a younger age than white women, and to develop more serious complications.[198] Nine times more women than men have lupus, and it also is more common in Hispanic, Asian, and Native American women.[199]

Clearly, these and the many other disproportionate burdens of disease, disability, and mortality experienced by racial/ethnic minorities and other low SES and disadvantaged population groups in the United States reinforce the importance of addressing health disparities through research, clinical care, public health, and health policy.

NIH Funding for Minority Health and Health Disparities Research

Actual NIH funding support levels for research on minority health were $2,396 million in FY 2008, and $2,592 million and $378 million in FY 2009, respectively, for non-ARRA (regular appropriations) and ARRA (Recovery Act appropriations). Actual NIH funding support levels for health disparities research were $2,614 million in FY 2008, and $2,806 million and $434 million in FY 2009, respectively, for non-ARRA and ARRA. There is substantial overlap in these funding figures. NIH funding for minority health and health disparities does not follow the standard RCDC process. These categories assign project funding according to populations tracked by gender or ethnicity. The databases used to track gender/ethnicity are complex and currently not compatible with the RCDC system. The table at the end of this chapter indicates the funding involved in this investment (see *Estimates of Funding for Various Research, Condition, and Disease Categories*.)

Summary of NIH Activities

NIH's commitment to reduce and ultimately eliminate health disparities in the United States is manifested in a wide variety of programs focused on: (1) Research, (2) Outreach, (3) Research/Outreach, (4) Research Training, and (5) Research Capacity. Given the multifactorial causes of health disparities, the complex array of their manifestations in vulnerable populations, and the multidisciplinary approaches required to effectively address them, many NIH programs are highly collaborative and cross-disciplinary, both within NIH and in partnership with external organizations. This section illustrates some of the currently funded initiatives.

Research

Basic, Clinical and Translational Research

NIH conducts and supports basic, clinical, and translational research designed to explain the relationship between disease and disparities, and improve patient quality of life. As knowledge increasingly is gained about the causes, mechanisms, natural histories, prevention, and treatment of diseases associated with known disparities, the ability to move important scientific discoveries effectively and efficiently from the bench to the bedside, and from the bedside to the community, will be a vital element in the ongoing campaign to reduce and eliminate health disparities in the United States. Research describing genetic vulnerabilities to specific diseases among specific populations is becoming a particularly fruitful area. Several initiatives are employing the rapidly advancing technological tools of modern genomics, such as genome-wide association studies (GWAS), linkage analysis, and direct sequencing, to discover the genetic variations involved in susceptibility to disease (also see the section on *Genomics* in Chapter 3 for more information about GWAS).

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For example, NIH support of research, disease registries, biological sample repositories, and collaborative initiatives with European researchers has advanced significantly our understanding of the genetic underpinnings of lupus. Lupus is an autoimmune disease that strikes women predominantly (nine times as often as men), and African American women at a rate three times that of white women. Numerous lupus risk genes have been identified recently, reflecting the complex expression of the disease, which varies from patient to patient. Among other translational efforts, methods are being developed to analyze individual patients' blood samples to group disease-specific variations in gene expression according to pathogenic mechanisms, which may be used to predict flares of lupus activity and eventually help guide individualized treatment.

The Centers of Research Translation (CORT) program is designed to help translate basic research discoveries into clinical trials for diagnostic approaches and treatments. One of the currently funded centers focuses on scleroderma, a disabling disease characterized by hardening of tissues in many parts of the body, including skin, internal organs, and blood vessels. There is a higher prevalence in some American Indian populations. Using functional genomics and gene networks, investigators at the center are studying the molecular basis of the disease to understand its underlying causes. Two other centers are focused on lupus research: one on the role of different cell types in the origin and development of lupus, and the other on examining the genetic underpinnings of the disease.

Chronic kidney disease (CKD) and diabetes also are the focus of intensive research efforts to associate genetic variations with increased disease risk. Scientists recently have identified a genetic region strongly associated with CKD that arises as a consequence of diseases other than diabetes, such as hypertension and HIV-associated kidney disease in African Americans. Another study is devoted to identifying and validating biomarkers and risk assessment tools for kidney function, injury, and disease progression in CKD patients, which will help assess disease risk and progression, and aid in early diagnosis. To help unravel the complex interactions between genes and environment involved with both type 1 and type 2 diabetes, NIH is supporting the Type 1 Diabetes Genetics Consortium and several major grants to study the genetics of type 2 diabetes. Studies have identified numerous genetic regions linked to both forms of the disease, while other studies concentrate on refining our understanding of how these genetic variations affect disease risk, particularly in specific racial/ethnic groups disproportionately affected by type 2 diabetes.

Characterizing gene-environment interaction to better understand disease risk factors also is at the heart of the Genetics of Coronary Artery Disease in Alaska Natives Study. The study not only is discovering relevant genes through genomic studies in a cohort of large Alaska Native families, but also is exploring the impact of changing lifestyle and diet on disease risk. Researchers have described rapidly increasing risk for coronary artery disease as villagers' lifestyles and diets have become increasingly westernized.

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The AIDS pandemic has proven to be one of the most significant challenges faced by the biomedical research community. In the United States, this devastating illness has heavily burdened racial and ethnic minorities and other medically underserved populations. NIH has made a significant investment in research to explain basic HIV biology. The NIH-sponsored Center for AIDS Health Disparities Research (CAHDR) at Meharry Medical College currently is investigating the biological basis for HIV/AIDS disparities among racial and ethnic groups. Recent CAHDR basic and translational research have explained the role of cholesterol in HIV entry into and replication within the cell. CAHDR investigators also have identified a microbial agent, betacyclodextrin (BCD), that can inactivate HIV and also make cells resistant to infection by removing cholesterol from the cell. This important discovery holds the hope that antimicrobial compounds such as BCD may be used as microbicides to protect women against HIV infection. The NIH-funded Meharry Translational Research Center will continue to investigate the varied reliance on cholesterol for survival and its

implications for developing potential new treatments for HIV infections and for treating AIDS patients with lipid imbalances.

Epidemiological/Population Research

Epidemiological and population research contribute significantly to efforts to eradicate health disparities by providing important knowledge designed to help identify, quantify, and characterize health disparities among populations; to test and monitor the effectiveness of potential interventions; and to monitor the health status of racial/ethnic minority groups. NIH fosters considerable research in this area across a wide range of conditions, disciplines, and health disparities populations.

For example, the NIH Inner-City Asthma Consortium (ICAC), launched in 2002, consists of 10 academic clinical centers designed to develop and carry out a long-range scientific plan to prevent asthma and reduce its severity in children living in the inner city where the prevalence and severity of asthma is particularly high. ICAC members are investigating the mechanisms underlying the onset and progression of asthma in this population, and are conducting research to develop diagnostic and prognostic biomarkers. ICAC researchers also are conducting clinical trials of promising immune-based therapies.

Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study is an observational study to explore the role of racial/ethnic and geographic differences on stroke risk factor prevalence and stroke incidence and mortality. Recruitment of the main REGARDS cohort was completed in 2007, with more than 30,000 participants enrolled. The group is 41 percent African American and 59 percent white, 55 percent female and 45 percent male. A number of important findings already are emerging that partially explain why African Americans and people in the so-called “Stroke Belt” in the southeastern United States are at higher risk of dying from stroke.

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The Collaborative Psychiatric Epidemiology Surveys (CPES) are large national surveys exploring the prevalence and characteristics of mental health disorders in the United States, and are contributing important information on disparities in the incidence of psychiatric illnesses and mental health service usage and access among racial/ethnic minorities. This effort includes the National Comorbidity Survey-Replication, the National Latino and Asian American Study, and the National Survey of American Life (NSAL), which focuses on the African American population. An important recent finding from the CPES NSAL study is that African American teens, especially girls, are at increased risk for suicide attempts, even if they have not been diagnosed with a mental disorder.[200] Such important results will lead to the development of interventions targeted at the populations at highest risk and to more efficient utilization of precious resources.

NIH has established a large-scale prospective study to elucidate the role of prenatal alcohol consumption and other maternal risk factors in three devastating pregnancy outcomes—fetal alcohol syndrome, sudden infant death syndrome, and stillbirth. The Prenatal Alcohol, Sudden Infant Death Syndrome (SIDS), and Stillbirth (PASS) Research Network will follow 12,000 pregnant, high-risk, American Indian and South African women and their infants until the infants are 12 months old. Since fetal alcohol syndrome was first recognized in 1970, NIH has supported epidemiological and clinical research in this area.

Outreach

NIH outreach initiatives encompass a wide range of endeavors, including communications and education programs, partnerships and collaborations with public and private organizations, and enhancement and expansion of access to information and services among disadvantaged populations. Outreach initiatives span many forms of activity, from creation of a new slogan to promote early stroke awareness, to efforts to disseminate science-based oral health information to specific populations, to health information outreach initiatives targeting high school students, and to a new, decade-long program devoted to environmental public health. They also address diverse stakeholder audiences, including students, patients, health care providers, public health educators and officials, policymakers, professional and patient advocacy organizations, and community-based groups. Information and interventions may target specific diseases and conditions such as HIV/AIDS, diabetes, digestive tract diseases, and SIDS, or they may be oriented toward a particular health disparities population subgroup, or both. These include a variety of NIH health information websites, several of which are available in Spanish (e.g., http://www.cancer.gov/espanol, http://medlineplus.gov/spanish/, http://aidsinfo.nih.gov/infoSIDA/).

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"Stroke strikes fast. You should too. Call 9-1-1." is the new action-oriented message being promoted by NIH in coordination with the Brain Attack Coalition, launched in May 2009 during Stroke Awareness Month.[201] This important educational initiative is just one small part of a grassroots educational campaign, Know Stroke in the Community, being conducted by NIH and CDC. The program encourages community leaders to become "Stroke Champions" and educate their neighbors about the signs and symptoms of stroke. It focuses on reaching African Americans, Hispanics, and seniors at high risk for stroke, as well as their family members, caregivers, and health care providers. As of the summer of 2009, Know Stroke has been launched in 12 cities and has educated 184 Stroke Champions who have conducted more than 600 community events. In 2007, NIH initiated a related stroke outreach program specifically targeted at Hispanics, who have a higher rate of risk factors for stroke and often face cultural and/or language barriers to prompt treatment, which is so crucial to achieving a positive outcome in the event of a stroke. The program's key component is a toolkit, *Ataque cerebral: conozca los sì ntomas y actùe a tiempo (Know Stroke. Know the Signs. Act in Time),* which can be used by *promotores de salud* (lay health educators) in *charlas* (health talks) to educate communities about the signs of stroke and the importance of calling 911 promptly to receive appropriate medical treatment.

NIH outreach also is tailored to meet the needs of specific groups or it may be designed to address the group itself or those who provide treatment or services to a group. Science-based oral health information disseminated by two NIH programs illustrates this point. A new Spanish-language website increases access to science-based oral health information among Hispanics. The site was recently tested in two cities to ensure that it is understandable, credible, and attractive to the intended audience of Spanish-dominant and bilingual Hispanics with backgrounds from different countries of origin and with varying levels of education. Dentists, dental hygienists, and caregivers have learned how to better serve the oral health needs of people with developmental disabilities through an online continuing education (CE) program called Practical Oral Care for People with Developmental Disabilities. The modules have proven so popular that NIH has extended the CE credit through 2011.

Sometimes outreach can be as simple as making new, innovative connections to reach particular audiences, but naturally, such initiatives often can be quite ambitious at the same time. Take the Science Education Partnership Award (SEPA) Program, which fosters relationships among educators, museum curators, and medical researchers to encourage the development of hands-on, inquiry-based curricula that inform students about timely issues such as obesity, diabetes, stem cells, and emerging infectious diseases. Through its exhibits at science centers and museums, SEPA introduces tens of

thousands of young students, including those from underserved communities, per year to careers in the biomedical sciences. In FY 2008, SEPA supported 68 projects, 50 of which were for middle and high school students, and 18 were based at science centers and museums. Spectrum: Building Pathways to Biomedical Research Careers for Girls and Women, a SEPA-funded program at San Francisco State University, connected girls of color in high school and middle school with women of color who are biomedical research trainees or faculty members and provided them and other underrepresented groups with materials about biomedical research careers.

NIH also brings timely and important health information to students in rural schools, and ultimately to their communities. The Peer Tutor High School Program in the Lower Rio Grande Valley of Texas, a school-based collaborative outreach program, is training high school Peer Tutors in the National Library of Medicine's online health resources, and then empowering them to teach other students and to disseminate health information to the local community. The majority of peer tutors and students in participating schools are Hispanic. Initiated more than 5 years ago, this program has trained more than 50 peer tutors who have conducted outreach to more than 2,500 high school students in the Lower Rio Grande Valley. The program has engaged the Biblioteca Las Amè ricas high school librarians in a leadership role to bring together students, faculty, administrators, and community leaders in promoting important online access to useful health information. This program currently is being replicated in other health disparity communities. Another unique program uses advanced Internet connectivity to electronically bring together Alaska Native students from a remote area of Alaska with predominantly Hispanic and African American students in inner-city Los Angeles for curriculum-based classroom lectures by scientists and information-sharing among the students.

Partnerships play a major role in NIH outreach. Working with religious organizations has been a useful method of reaching rural, minority, and other underserved groups. NIH sponsors the Consumer Health Resource Information Service (CHRIS) Program with church ministries in Tennessee to improve information access and health literacy related to the high incidence of disease in those communities. A long-standing NIH partnership with the United Negro College Fund Special Programs Corporation promotes capacity-building, improved information access, and community outreach on Historically Black Colleges and University (HBCU) campuses and surrounding communities.

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The NIH Partnerships for Environmental Public Health Program (PEPH), a 10-year umbrella program, currently is bringing together scientists, community members, educators, health care providers, public health officials, and policymakers to promote science-based investigations of environmental health threats that affect communities at local, regional, and national levels. By promoting environmental public health research and dissemination over the next decade, NIH will lead the effort to educate vulnerable populations about the dangers of exposure to occupational or environmental hazards.

Research/Outreach

NIH frequently supports projects that incorporate a mix of elements devoted to both research and outreach. These activities often intermingle, and may involve one or more outreach elements such as education, awareness, recruitment of study/clinical trial participants, and a variety of clinical and preventive interventions, often translational in nature. In many initiatives, information and interventions are provided to targeted populations on a pilot basis so that researchers can collect valuable data and feedback on how effectively the initiative is addressing the problem of interest. Community-based participatory research (CBPR) is an increasingly important component of many such projects. The CBPR approach ensures that various stakeholders (community members, key organizational representatives, health care delivery team members, decisionmakers, and researchers) participate as full partners in scientific research to improve the health of communities.

NIH is supporting the development, implementation, and evaluation of intervention research by using CBPR principles and methods to target diseases of major public health interest such as obesity, diabetes, cancer, hypertension, HIV/AIDS, and mental health issues such as suicide and alcohol abuse in health disparity communities. The NCMHD Community-Based Participatory Research Program promotes participatory research collaborations that are equal partnerships between community organizations and members of the research community in all stages of the research process. This long-term program supports a 3-year planning phase, a 5-year intervention phase, and a 3-year dissemination phase. The initiative began in FY 2005 with the award of 25 3-year research planning grants. In FY 2008, 40 5-year intervention research grants were awarded. Competitive 3-year dissemination grants will be made in 2013.

CBPR principles as they apply to health disparities research are the driving force behind the NCMHD Centers of Excellence Program. Since its inception, this congressionally mandated program has created hundreds of unique partnerships to improve the health of racial/ethnic minorities and other health disparity populations by forging ties with hospitals, tribal groups, health plans, health centers, community- and faith-based organizations, civic and nonprofit health organizations, and local, city, and state governments. The centers and their associated grants now are located in 32 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. NIH supported 49 centers in FY 2008 and 51 in FY 2009; in May 2009, NIH issued an RFA using ARRA funds to support centers with a 2-year project period, as opposed to the traditional 5 years. The Centers of Excellence, with their community partners, have contributed substantially to scientific knowledge and lay understanding of health disparities. Other CBPR programs funded by NIH include the Community Networks Program to Reduce Cancer Health Disparities Through Education, Research and Training (CNP). A total of 25 institutions were funded under this 5-year program to reduce cancer disparities in racial/ethnic minorities and underserved populations by increasing access to and use of beneficial biomedical procedures in primary and secondary prevention, and to develop a cadre of well-trained researchers who will continue to reduce disparities in communities.

In some instances, programs combining research and outreach will target a particular problem in a particular population. That was the case in a recent initiative studying the oral health of rural California Latino preschoolers. Researchers explored how the interactions among family, community, providers, and regulators led to oral health disparities among this cohort of children. For example, caregivers were found to not always recognize signs of tooth decay among their children. Access to care was difficult due to fluctuating insurance eligibility, lack of public transportation, and other factors. There also was a lack of dentists willing to serve rural low-income populations. The empirical research associated with these and many more observations has contributed to understanding that multiple intersecting factors at numerous levels should inform intervention research targeted to the individual, the community, and society. Another example of this is the Patient Navigation Research Program (PNRP), which is designed to examine effective ways to engage health providers and health systems to ensure that racial/ethnic minority and underserved Americans receive appropriate cancer screening, diagnosis, and treatment in a timely manner. Although anyone may benefit from Patient Navigation services, the primary participants for this research program are populations experiencing cancer health disparities, such as racial/ethnic minorities, individuals with lower SES, and residents of rural areas.

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Many programs use important research findings as the basis for designing effective outreach efforts and targeted interventions. For example, NIH, along with multiple Federal agencies and health and social service professionals, systematically is moving science-based substance abuse treatment interventions into the criminal justice system, where improvements are sorely needed. Research has suggested that prisoners who receive prison-based treatment may be more likely to remain drug-free upon their release. Similarly, new research has shown that among HIV-positive prisoners who begin treatment in prison, simply providing them help with paperwork to receive their medications can promote greater continuity of HIV pharmacotherapy upon release. In this instance, research informing outreach may reduce drug use and

criminal recidivism, and help limit the spread of HIV in communities—all potentially significant social and public health accomplishments.

Research Training

To ensure that the next generation of biomedical scientists is broadly diverse and to build upon the substantial existing body of knowledge regarding the causes and potential amelioration of minority health and health disparities, NIH supports many research training programs, both intramural and extramural. NIH research training programs promote diversity in the biomedical research workforce to increase the pool of scientists from diverse backgrounds underrepresented in this field, including persons from disadvantaged backgrounds, individuals from racial/ethnic minority groups, and persons with disabilities.

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A FY 2008 program announcement, Research Supplements to Promote Diversity in Health-Related Research, launched an NIH-wide initiative to promote diversity in the biomedical, behavioral, clinical, and social sciences research workforce. This program is designed to provide support for research experiences for individuals from diverse backgrounds underrepresented in biomedical research throughout the continuum from high school through the faculty level. NIH expects that these efforts to diversify the workforce will: (1) lead to recruitment of the most talented researchers from all groups; (2) improve the quality of the educational and training environment; (3) balance and broaden perspectives in setting research priorities; (4) improve the ability to recruit subjects from diverse backgrounds into clinical research protocols; and (5) improve the Nation's capacity to address and eliminate health disparities.

NIH developed the Short-Term Education Program for Underrepresented Persons (STEP-UP) Program to expose students from diverse backgrounds underrepresented in biomedical research. The long-term goal has been to increase the pool of underrepresented and disadvantaged students "in the pipeline" who are committed to a career in biomedical, behavioral, clinical, or social science research. To accomplish this goal, the STEP-UP program has provided research education grants to institutions for the support of eligible high school and undergraduate students with research education and training opportunities that will develop both their research capabilities and their interest in pursuing a career in research. The institutions provide administrative support for the STEP-UP program and its student participants throughout the summer research experience.

The Minority Health and Health Disparities International Research Training (MHIRT) Program supports the ability of health professions programs at U.S. academic institutions to offer short-term international training opportunities in health disparities research to undergraduate and graduate students who are from health disparity populations and/or groups underrepresented in the research enterprise. By developing a cadre of researchers who better understand health disparities issues from a global perspective, MHIRT contributes to the eventual elimination of health disparities in the United States. In 2009, the MHIRT program made awards to 22 academic institutions, with grantees traveling to work with international investigators in 41 countries.

The Minority Institution/Cancer Center Partnership (MI/CCP) Program enables minority-serving institutions (MSIs) and NCI-designated Cancer Centers to train scientists from diverse backgrounds in cancer research and to effectively deliver cancer advances to racially and ethnically diverse communities. The program is designed to facilitate planning and implementation of focused partnerships in cancer-related research, training, career development, education, and/or outreach. These partnerships foster and support intensive collaborations to develop stronger cancer programs aimed at understanding the reasons behind significant cancer health disparities among racial/ethnic minorities and socioeconomically disadvantaged populations. The Continuing Umbrella of Research Experiences (CURE) Program offers

funding opportunities to support training and career development for students, researchers, and junior investigators using research supplements, predoctoral fellowships, and career development awards. The CURE program promotes unique training and career development opportunities to enhance diversity in cancer and cancer health disparities research. With a focus on broadening the cadre of investigators from diverse backgrounds engaging in cancer research, the CURE program identifies promising candidates from high school to junior investigator levels and provides them with a continuum of competitive funding opportunities.

The Minority Institution/Cancer Center Partnership program enables minority-serving institutions and NCI-designated Cancer Centers to train scientists from diverse backgrounds in cancer research and to effectively deliver cancer advances to diverse health disparity communities.

The Loan Repayment Programs also help to enhance the diversity of the Nation's biomedical research workforce by alleviating financial barriers for students from diverse backgrounds, including racial/ethnic minority and other scientists from health disparity populations, particularly those pursuing research careers focused on health disparities. The Loan Repayment Program for Health Disparities Research encourages qualified health professionals to pursue biomedical, clinical, behavioral, and health services research careers. At least 50 percent of the awards are required by law to go to participants from health disparity populations. The Extramural Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds works to increase the participation of eligible individuals in clinical research. In 2009, NCMHD made awards to 314 individuals.

Research Capacity

Another important facet of the NIH mission to reduce and ultimately eliminate health disparities in the United States is the ongoing effort to increase and build the capacity of academic institutions to conduct health disparities research. A number of NIH programs expand training opportunities, foster career development, and increase funding for health disparities research. Projects provide resources to recruit, retain, and provide career development to scientists from diverse health disparity populations, and to expand the pool of investigators eligible to pursue health disparities research.

For example, the Research Centers in Minority Institutions (RCMI) Program, which began in 1985 in response to congressional report language, provides a variety of awards to minority-serving institutions to improve research capacity and reduce health disparities. Funds are used to acquire advanced instrumentation, renovate laboratories, and improve research infrastructure, as well as to enhance faculty development and support pilot projects and core facilities. Recently, some RCMI centers have established connections with nearby consortium members of the Clinical and Translational Science Award (CTSA) institutions, enhancing the research capacity at both RCMI centers and CTSA institutions. For example, such collaborations have been established between Emory University and Morehouse School of Medicine (Atlanta), Vanderbilt University and Meharry Medical College (Nashville), and Weill Cornell Medical College and Hunter College (New York) (also see the section on *Clinical and Translational Research* in Chapter 3).

The Research Infrastructure in Minority Institutions (RIMI) program (which will be replaced by the Building Research Infrastructure and Capacity [BRIC] program in FY 2010) directly addresses the need to strengthen the research environment at academic institutions with unique missions and a demonstrated commitment to the needs of health disparity populations, including small junior colleges, tribal colleges and universities (TCUs), and other schools that only offer associate's, bachelor's, and/or master's degrees.

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offer associate's, bachelor's, and/or master's degrees. Grant support helps: to develop or expand existing capacities for research programs (both institutional and individual investigator-driven) that address health disparities; to establish developmental training programs for faculty and students; and to develop collaborations with larger, more research-intensive universities.

The NCMHD Research Endowment Program is a unique congressionally mandated (Pub. L. No. 106-525) initiative that promotes minority health and health disparities research capacity-building at eligible academic institutions by providing grant funds that are applied directly to an institution's endowment. The interest on that investment must be used to acquire and upgrade equipment and information technology; recruit diverse faculty and develop courses related to minority health and health disparities; and enhance the recruitment and retention of students from diverse backgrounds, including racial/ethnic minority and other students from health disparity populations who are underrepresented in the scientific workforce.

The Institutional Development Award (IDeA) Program improves the competitiveness of investigators in 23 states and Puerto Rico with historically low NIH funding by supporting multidisciplinary centers and statewide collaborative partnerships that increase institutions' capacities to conduct cutting-edge biomedical research. Research supported through this program helps to reduce health disparities in racial/ethnic minority populations, including American Indians, Alaska Natives, Hispanics, Native Hawaiians, and other Pacific Islanders within IDeA states. IDeA has been particularly supportive of efforts to increase connectivity, bandwidth, and access to high-performance computational resources through IDeANet, an Internet-based network providing connectivity for high-bandwidth science applications. For example, cyber infrastructure in six northwestern states (Alaska, Hawaii, Idaho, Montana, Nevada, and Wyoming) has been improved dramatically by the Lariat Networking Project. Five other IDeA states (Delaware, Maine, New Hampshire, Rhode Island, and Vermont) recently formed the North East Cyberinfrastructure Consortium. Ultimately, the IDeANet initiative will enable all institutions in the IDeA program to engage in national and international collaborations.

Conclusion

Reducing and ultimately eliminating health disparities in the United States remains one of NIH's top priorities in its efforts to improve and protect the health of all Americans, and research remains a fundamental aspect of the national strategy to meet this challenge. NIH will continue to support and conduct a broad range of biomedical and behavioral research focused on relevant diseases and conditions occurring with increased frequency or severity or with worse outcomes in racial/ethnic minorities, rural populations, groups with low income, and other health disparities populations. By accelerating the translation of scientific advances into clinical practice and implementing sound health promotion interventions in communities most affected by health disparities, NIH hopes to eliminate health disparities in affected communities and realize the vision of a world where all will have the opportunity to lead long, healthy, and productive lives.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Basic, Clinical, and Translational Research

Compliance with the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research: NIH works to ensure compliance with the NIH Policy for the Inclusion of Women and Minorities as Subjects in Clinical Research by convening a trans-NIH committee that addresses consistency in inclusion policy implementation and investigator reporting of population data. Over the past 2 years, NIH has focused on analyzing and streamlining the data reporting process, reemphasizing the vital role of NIH staff to monitor adherence of the NIH Inclusion policy and management of grants, contracts, and cooperative agreements that involve human subjects research. The role of peer reviewers and investigators in meeting policy requirements continues to be stressed. NIH compiled the annual aggregate comprehensive reports: *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research* and the *2009 Biennial Report Certifying IC Compliance with the Inclusion Guidelines* based upon IC Advisory Council reviews, as required by statute.

→ For more information, see http://orwh.od.nih.gov/inclusion.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E/I) (**ORWH**, OER, OIR)

Translating Basic Science into New and Better Treatment for HIV/AIDS: The HIV/AIDS pandemic has proven to be one of the most significant challenges faced by the biomedical research community. In the United States this devastating illness heavily has burdened racial and ethnic minority populations and other medically underserved populations. NIH has made a significant investment in research to elucidate basic HIV biology. The Center for AIDS Health Disparities Research (CAHDR) is engaged in research to understand the biological basis for HIV/AIDS disparities among racial and ethnic groups. The overall mission is to develop interventions that will help eliminate the disparities, and ultimately benefit all people at risk of HIV/AIDS. Recent basic and translational research in the CAHDR has focused on understanding how the virus exploits certain cellular proteins for its own purposes and how it hijacks cellular machinery. A particular focus of the research has examined the role of cholesterol in HIV biology. Cholesterol is critical to many cellular processes, including the fusion of cells to one another. Fusion is how HIV enters cells, and CAHDR research has shown that cholesterol controls the fusion of HIV to cells, and also controls the production of new HIV particles by infected cells. Findings also have revealed that HIV emerges from areas of the cell membrane rich in cholesterol, causing the virus itself to be rich in cholesterol. CAHDR investigators also have demonstrated that the sugar betacyclodextrin (BCD) can inactivate HIV and also make cells resistant to infection by removing cholesterol. This sugar, in one form or another, is used widely in consumer products such as food and cosmetics, and also is used by major pharmaceutical companies as a carrier for drugs. As such, BCD has a proven and extensive safety record of use in humans and has major potential as a prophylactic against HIV to be used in the form of a vaginal microbicide (a gel or cream that would protect

women against infection). The most recent work has found that a protein controlling the activation of HIV genes is itself controlled by the levels of cholesterol in a cell. This means that cholesterol directly influences the genetic replication of HIV. The NIH-funded Meharry Translational Research Center will continue to investigate HIV's varied reliance on cholesterol for survival and its implications for developing potential new treatments for HIV infections and for treating AIDS patients with lipid imbalances.

→ (E) (**NCRR**)

Centers of Research Translation (CORT): The NIH CORTs are designed to bring together basic and clinical research to translate basic discoveries into new drugs, treatments, and diagnostics. Each CORT encompasses at least three projects, including one clinical and one basic research study. The centers are:

- The Center for Translating Molecular Signal Pathways to Orthopaedic Trauma Care studies the biological basis of fracture healing and the efficacy of a potential new treatment, teriparatide, an injectable form of human parathyroid hormone that stimulates new bone formation.
- The Center for Lupus Research investigates the role of different cell types in the origin and development of lupus, markers of disease activity and severity, and new targets for treatment.
- The Center for X-Linked Hypophosphatemic Rickets Research focuses on the various molecular contributors to this genetic form of rickets, and works toward developing new treatments.
- The Center for Research Translation in Scleroderma is studying the molecular basis of scleroderma to understand its underlying causes, using functional genomics and gene networks.
- The Center for Genetic Dissection of Systemic Lupus Erythematosus (lupus) studies mouse models of lupus to identify the genetic background of developmental stages of the disease.
- The Center for New Approaches to Assess and Forestall Osteoarthritis in Injured Joints is developing new methods of forestalling post-traumatic osteoarthritis (PTOA).
- The Center for Psoriasis Research Translation uses a Phase I mechanistic, safety, and preliminary efficacy study to test a novel photodynamic therapy for psoriasis.

→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/11_08.asp
→ For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2007/corts.asp
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAMS**)

Behavioral and Social Science Research on Understanding and Reducing Health Disparities: NIH, with CDC, issued two program announcements with review to fund behavioral and social sciences research on health disparities. These announcements called for research to improve and elaborate explanations and understandings of the causes for health disparities. In so doing, the announcements stressed the explicit employment of concepts and models from the behavioral and social sciences to guide basic and applied research by focusing on three action areas: Public Policy, Health Care, and Disease/Disability Prevention. They emphasized basic research on the behavioral and social (acting with or through biological) pathways that give rise to disparities in health and applied or translational research on the development, testing, and delivery of interventions to reduce disparities. They encouraged a multilevel analytic framework in investigating public health issues and their interactions (e.g., multiple morbidities rather than single illnesses), as well as attention to risk factors or causal processes common to various health conditions (e.g., smoking, diet, exercise, and access to health care). To date about 30 projects have been funded. In 2009, the Economic and Social Research Council of the United Kingdom and NIH issued a joint call for applications and funded six additional research grants involving collaborations between American and British research teams.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-379.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-380.html

→ For more information, see http://esrcsocietytoday.ac.uk/ESRCInfoCentre/opportunities/international/esrc-nih.aspx
→ (E) (**OBSSR**, NCI, NIA, NIAAA, NICHD, NIDDK, NINR)

Medical Technologies that Reduce Health Disparities: Appropriate medical technologies should be effective, affordable, culturally acceptable, and deliverable to those who need them. NIH is funding a research initiative to support the development of appropriate medical technologies for underserved settings. To ensure that the technology is appropriate, applications must involve interactions with underserved populations and/or collaborations with clinics in an underserved community.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-09-001.html
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIBIB**, NCMHD, NCRR, NIMH)

Cancer Health Disparities Research Programs and Initiatives: NIH has expanded research on the basic biologic factors of cancer disparities to provide a foundation for minimizing risk, identifying targets, developing preventive and therapeutic interventions, and understanding how genetic susceptibility may be influenced by social, economic, race/ethnicity, and geographic factors. Thus, the research programs involve multidisciplinary teams, which contribute to understanding the etiology of cancer and build prevention and intervention evidence-based models to eliminate cancer disparities. Several programs at NIH address disparities along the cancer continuum from prevention to survival.

- The trans-disciplinary Geographic Management Program (GMaP) pilot initiative builds regional networks to support research, training, and infrastructure to develop state-of-the-art networks/centers to ensure a continuous supply of high-quality human biospecimens from multi-ethnic communities.
- The Community Networks Program engages communities experiencing cancer disparities to design, test, and evaluate evidence-based strategies to address critical needs, such as access to screening, mentoring, and training; policy development; and community outreach and education.
- The Patient Navigation Research Program builds partnerships to ensure that racial/ethnic minorities and underserved populations with abnormal cancer screening results receive appropriate care.
- The Community Clinical Oncology Program is a network for conducting cancer prevention and treatment clinical trials by connecting academic centers with community physicians.
- The NIH Centers for Population Health and Health Disparities catalyze transdisciplinary research to improve the understanding of complex interactions of biological, social, cultural, environmental, and behavioral factors that contribute to health inequities, and to develop and implement novel intervention strategies that are multilevel and multifactorial.
- The Tobacco Research Network on Disparities' mission is to understand and address tobacco-related disparities by advancing the science, translating that scientific knowledge into practice, and informing public policy.
- The Centers of Excellence in Cancer Communication Research continue to use best practices in communication science to extend the reach of biomedical benefits equitably throughout the population.

→ For more information, see http://crchd.cancer.gov/
→ For more information, see http://crchd.cancer.gov/cnp/background.html
→ For more information, see http://crchd.cancer.gov/pnp/pnrp-index.html
→ For more information, see http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html
→ This example also appears in Chapter 2: *Cancer*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCI**)

Lupus: There have been significant advances in identifying disease risk genes for systemic lupus erythematosus (lupus) in recent years. Genome-wide association, linkage analysis, and direct sequencing have revealed genetic variations in lupus patients for molecules involved in immune mechanisms and regulation, inflammation, and vascular cell activities. The

disease affects women disproportionately, with female lupus patients outnumbering males nine to one. African American women are three times as likely to get lupus as Caucasian women, and it also is common more in Hispanic, Asian, and American Indian women. These results are being replicated in distinct racial and ethnic populations. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects. Another critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by government agencies, private foundations, and industry. The numerous genes uncovered in these studies reflect the complex expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene specifically is associated with severe forms of lupus that include kidney disease, but not skin manifestations. Methods to analyze patients' blood samples are being developed to group disease-specific variations in gene expression according to pathogenic mechanisms. This system may be used to predict flares of lupus activity in the future and guide individualized treatment. Lupus risk genes also have been discovered on the X chromosome and reproduced in animal models of the disease. These important findings shed light on the female predominance of lupus.

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→ This example also appears in Chapter 2: *Autoimmune Diseases*, Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAMS**, NCI, NCRR, NHLBI, NIAID, NIDCR, NINDS)

Diabetes Prevention Program Outcomes Study (DPPOS) and Translational Research: The landmark NIH Diabetes Prevention Program (DPP) clinical trial showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk. This finding was true across all participating ethnic groups and for both men and women. The DPPOS is a long-term follow-up study of the DPP participants that is determining the durability of the interventions in preventing or delaying type 2 diabetes, and how the interventions affect the development of cardiovascular disease and other complications of diabetes. The DPP group was highly diverse (45 percent from minority ethnic and racial groups), and DPPOS will compare outcomes for women and men, and by age and ethnicity. Renewed in FY 2009 for a second 5-year phase, the DPPOS will enable researchers to better determine the lasting benefits of the interventions to diabetes prevention and/or the delay of onset. In addition, NIH is pursuing translational research efforts to develop more cost-effective methods of achieving the lifestyle change that delayed or prevented diabetes in the DPP, and better methods to identify those with prediabetes. For example, one translational effort is using the YMCA to deliver a DPP lifestyle intervention; data from a recent pilot study suggest that using the YMCA may be a low-cost way to deliver a lifestyle intervention to large numbers of people in the United States. Many of these translational research studies focus on minority populations disproportionately burdened by type 2 diabetes and by obesity, a significant risk factor for type 2 diabetes.

→ For more information, see http://www.bsc.gwu.edu/dpp/protocol.htmlvdoc
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-09-176.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-06-532.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**, CDC, IHS, NEI, NHLBI, NIA, NICHD, NINR, OBSSR, ORWH)

Look AHEAD (Action for Health in Diabetes): This NIH-led, multicenter, randomized clinical trial is examining the long-term health effects of an intensive lifestyle intervention (ILI) designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity. The study enrolled more than 5,100 overweight or obese adults with type 2 diabetes. Results from the first year of the study showed that participants in the ILI group achieved clinically significant weight loss; this was the case across all subgroups of the ethnically and demographically diverse study population. In addition, this weight loss was associated with an increase in "health-related quality of life" and improved cardiovascular fitness, blood pressure, cholesterol, and blood glucose, as compared to a control group receiving diabetes support and education. As another major point for health outcome measurement, the study recently completed 4 years of intervention and follow-up. In the coming years, continued follow-up of the Look AHEAD participants will show whether the ILI can reduce the incidence of heart attack and stroke and improve other health-related outcomes in this population. These findings will have important implications for treating type 2 diabetes.

→ For more information, see http://www2.niddk.nih.gov/Research/ClinicalResearch/ClinicalTrials/Patients/ClinicalResearchLookahead.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIDDK**, CDC, NCMHD, NHLBI, NINR, ORWH) (GPRA)

Genetics of Diabetes: Diabetes is a common, potentially deadly and debilitating chronic disease that poses an enormous health care burden. Both of the most common forms of diabetes, type 1 and type 2, are caused by an intersection of genetic and environmental risk factors. Although genetic effects on developing diabetes are profound, they are not simple, as there are many genes that influence the likelihood of developing type 1 or type 2 diabetes. Further, ethnicity impacts both genetic and environmental risk factors. To learn more about diabetes genetics, particularly through new genomic technologies, NIH supports the Type 1 Diabetes Genetics Consortium to study type 1 diabetes, and several major grants to study the genetics of type 2 diabetes. These programs now have identified at least 40 genetic regions linked to type 1 diabetes and at least 38 type 2 diabetes genes. Other studies are refining our understanding of how these genes affect diabetes risk. Many of these projects are geared to collect data from multiple ethnic groups, but a recent initiative sought to advance knowledge of diabetes risk genes in specific racial and ethnic groups disproportionately affected by type 2 diabetes, to understand how different genes affect different populations.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-004.html
→ For more information, see http://www.t1dgc.org
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
→ (E) (**NIDDK**, NHGRI, NIAID, NICHD)

Genetics of Chronic Kidney Disease: Researchers recently have made progress in uncovering the role of genetics in chronic kidney disease (CKD) arising from various causes. Scientists recently have identified a genetic region that is strongly associated with CKD in African Americans that arises as a consequence of conditions other than diabetes, such as high blood pressure and HIV-associated kidney disease. Several variants associated with the *MYH9* gene were identified as major contributors to excess risk of this kind of CKD among African Americans. This finding suggests that CKD may proceed along different paths depending on whether diabetes or another condition is the underlying disorder. The Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to study progression of an inherited form of kidney disease, polycystic kidney disease (PKD). Phase I of the study demonstrated that magnetic resonance imaging accurately could track structural changes in the kidneys; Phase II showed that patients with mutations in the *PKD1* gene have more cysts and larger kidneys than patients with *PKD2* mutations. A planned third phase of CRISP will provide critical information about the validity of changes in kidney volume as a surrogate marker for loss of kidney function. NIH also has launched a study to identify and validate biomarkers and risk assessment tools for kidney function, injury, and disease progression in patients with CKD, to predict risk, aid early diagnosis, and assess disease progression.

→ Kopp JB, et al. *Nat Genet* 2008;40(10):1175-84. PMID: 18794856.
Kao WHL, et al. *Nat Genet* 2008;40(10):1185-92. PMID: 18794854. PMCID: PMC2614692.
Grantham JJ, et al. *New Engl J Med* 2006;354(20):2122-30. PMID: 16707749.
Rule AD, et al. *J Am Soc Nephrol* 2006;17(3):854-62. PMID: 16452494.
→ For more information, see http://www.nih.gov/news/health/sep2008/niddk-14.htm
→ For more information, see http://www.nih.gov/news/pr/may2006/niddk-17.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
→ (E/I) (**NIDDK**, AHRQ, NCI, NCRR, NHLBI)

Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS): HANDLS is a community-based study to evaluate health disparities in socioeconomically diverse African American and white adults in Baltimore. Planned recruitment of 4,000 participants is more than three-quarters complete. Scientists are using mobile medical research vehicles to make possible onsite bone density and carotid artery imaging, physical examination and blood sampling, physical and cardiovascular performance, participant interviews, cognitive testing, and psychophysiological testing. HANDLS also will include studies of other variables, including: nutrition, environment and neighborhood effects, genetic make-up, family history, and access to health care. Participants will be followed over a 20-year period to allow researchers to gain insights into the physical, genetic, biologic, demographic, and psychosocial traits that may be most critical for healthy aging.

→ For more information, see http://handls.nih.gov
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIA**)

OAR Management and Coordination of Trans-NIH HIV/AIDS Research to Address the AIDS Epidemic in the United States: Every nine and a half minutes, someone in the United States is infected with HIV. It is estimated that in 2006, 56,300 people were newly infected with the virus. There are large disparities in the prevalence of HIV among different racial and ethnic populations. Black men and women, Hispanic men, and men who have sex with men of all races are impacted disproportionately by HIV. In 2006, blacks accounted for 45 percent of new infections and Hispanics for 17 percent, even though those populations comprised only 13 percent and 15 percent, respectively, of the U.S. population at that time. Moreover, the prevalence rate for black men was six times the rate for white men, and the rate for Hispanic men was more than twice that for white men. OAR leads the trans-NIH planning and coordination efforts in the area of AIDS research in racial and ethnic populations. A section of the annual Trans-NIH Plan for HIV-Related Research is specifically dedicated to research in this area. The Plan, developed in collaboration with scientific experts and community members, serves as a roadmap for the planning of AIDS-related research in this area. OAR also supports a multifaceted initiative to address the U.S. epidemic, particularly in racial and ethnic populations. For example, OAR has launched a new initiative to address the serious and complex AIDS epidemic in U.S. Hispanic populations through community outreach, regional workshops, leadership development, and research collaborations. In addition, OAR, in collaboration with NIAID and the NIH CC, has provided key support for a new trans-NIH initiative on AIDS in the District of Columbia, a city with large black and Hispanic populations and where 3 percent of the population is known to be infected with HIV.

→ Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2007. Vol. 19. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2009. Available at www.cdc.gov/hiv/topics/surveillance/resources/reports/. Accessed July 14, 2009.
Centers for Disease Control and Prevention. HIV Prevalence Estimates—United States, 2006. MMRW. 2008; 57(39);1073-1076. Available at www.cdc.gov/mmwr/preview/mmwrhtml/mm5739a2.htm. Accessed July 14, 2009.
→ For more information, see http://www.oar.nih.gov/strategicplan/fy2010/pdf/Chapter5.pdf
→ For more information, see http://www.nineandahalfminutes.org
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (O) (**OAR**)

Microbiome of the Lung and Respiratory Tract in HIV: Research grant applications were solicited in 2009 for studies to characterize the lung and respiratory tract microbiota in HIV-infected individuals and matched HIV-uninfected controls, using molecular and high-throughput techniques to identify bacteria and other organisms, including viruses, cell-wall deficient organisms, protozoa, and fungi. The characteristics and mix of organisms populating the respiratory tract, coupled with the state of local respiratory defenses, are key factors in determining whether a person remains healthy or develops infection. HIV-infected individuals are at very high risk of developing pneumonias caused by pathogenic and opportunistic microorganisms. These respiratory infections frequently cause morbidity, and they often are life-threatening. They also may increase the rate of replication of HIV, accelerating the course of HIV disease. HIV-infected individuals often experience decreased lung function following pneumonia which is not observed in normal, HIV-uninfected populations. Furthermore, lung infections and microbial colonization are suspected in the etiology of HIV-associated emphysema and pulmonary hypertension. Lung infections also may play a role in inducing the immune reconstitution syndrome seen in some HIV-infected patients following initiation of multidrug antiretroviral regimens. Knowledge of the role of the lung microbiome in preserving health or causing disease and the divergent effects observed in HIV-infected vs. uninfected individuals may lead to the identification of predictors of disease progression and therapeutic targets for translation into better preventive and treatment strategies.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-006.html
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NHLBI**)

Centers of Excellence Program: The congressionally mandated NCMHD Centers of Excellence Program leads the effort in supporting biomedical and behavioral research in minority health and health disparities research. Launched in 2002, this program has created new partnerships that enable institutions at all levels of research capability to initiate new research programs or build new institutional and community capacity for improving minority health, eliminating health disparities, providing research training, and engaging health disparity communities in efforts to improve their health. The Centers of Excellence Program has since its inception created hundreds of unique partnerships with hospitals, tribal groups, health plans, health centers, community- and faith-based organizations, civic and nonprofit health organizations, and local, city, and state governments. The research conducted by NCMHD Centers of Excellence and their community partners is expanding understanding of health disparities through numerous publications in the peer-reviewed scientific literature, press releases, television spots, websites, and local and regional newsletters; and training of community members as lay health advisors. The NCMHD Centers of Excellence and associated grants are located in 32 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. NIH supported 49 COEs in FY 2008 and 51 COEs in FY 2009. In May 2009, NIH issued RFA MD-09-007, "Recovery Act Limited Competition: NCMHD Center of Excellence (P20)" to establish COEs having a project period of 2 years compared to the traditional project period of 5 years. It is expected that Recovery Act funds will aid in stimulating the economy and seed the development of emerging research infrastructures capable of generating and supporting innovative partnerships, and creative program and research strategies for advancing minority health, eliminating health disparities, and attracting new funding streams; awards for this competition will be made in FY 2009. Currently funded examples of NCMHD Centers of Excellence program projects include:

- Insulin Resistance and Glucocorticoids
- Parent Diabetes Prevention Trial (STPDPT)
- The Right Question Project-Mental Health II
- Race and Ethnic Disparities in Mental and Cardiovascular Health Disorders: Stress, Self-Regulation of Health Behaviors, and the HPA-Axis
- Using Resistance Training to Reduce Metabolic and Cardiovascular Disease Risk in Obese Hispanic and African American Youth
- (E) (**NCMHD**)

Epidemiological/Population Research

The Strong Heart Study: The Strong Heart Study was initiated in 1988 to estimate the morbidity and mortality from cardiovascular disease (CVD) in 3 geographically diverse groups of American Indians and to estimate the levels of CVD risk factors in 4,549 adult men and women aged 45-74 in 3 centers. It evolved into a study of large families after a successful pilot study in each center. The original cohort was examined three times and continues to be followed for morbidity and mortality. The family study currently is completing its second examination and has conducted a linkage study of multiple cardiovascular phenotypes.

→ For more information, see http://strongheart.ouhsc.edu
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NHLBI**)

The Coronary Artery Risk Development in Young Adults (CARDIA) Study: CARDIA is studying the distribution and evolution of risk factors for cardiovascular disease (CVD) during young adulthood in 5,115 African-American and white men and women who were aged 18-30 years when the study began in 1985. The project has completed 7 examinations of these participants over 20 years. CARDIA has measured standard CVD risk factors at all examinations to permit analyses of secular trends and interrelationships among risk factors. Measures of subclinical CVD, such as coronary artery calcium, carotid intima-media wall thickness, arterial compliance, and left ventricular mass and function also have been assessed. DNA will be analyzed to elucidate how genetic variability and gene-environment interactions may explain differences in the severity and progression of CVD. Major objectives for the upcoming eighth examination include identifying early adulthood antecedents and consequences of obesity, understanding the determinants and trajectories of CVD development in women during the menopausal transition, and further assessing the basis for racial differences in the development and progression of CVD.

→ For more information, see http://www.cardia.dopm.uab.edu
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NHLBI**)

Genetics of Coronary Artery Disease in Alaska Natives Study: This is a study of large families of Alaska natives (Eskimos) living in Nome and surrounding villages. Recruitment of 1,214 individuals in approximately 40 families has been accomplished. A genome-wide scan of almost 400 microsatellite markers and linkage analyses with cardiovascular disease risk factors and subclinical disease measures were completed recently to search for relevant genes. Phase II is nearing completion and will establish surveillance of the cohort, add four villages that were part of a previous study following a similar protocol, conduct a second examination on the cohort, and pursue significant linkage findings.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NHLBI**)

The Multi-Ethnic Study of Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter epidemiological study of cardiovascular disease (CVD) in 6,914 men and women from 4 ethnic groups—white, African-American, Hispanic, and Chinese—who have been followed for almost 10 years to identify predictors of progression of subclinical CVD. The study originally was funded from 1999 to 2008 and subsequently renewed through 2015. It has measured and compared the predictive value of chest computed tomography, cardiac magnetic resonance imaging, carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for the development of CVD. MESA has major ongoing ancillary studies in the areas of air pollution (funded by the EPA), chronic lung disease, and genetics. MESA SHARe (SNP Health Association Resource) will combine genome-wide scans

with detailed phenotypic information and share these data with the scientific community for genome-wide association analyses.

→ For more information, see http://mesa-nhlbi.org
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*
→ (E) (**NHLBI**, NEI)

Reducing Disparities in Stroke: NIH actively is engaged in a number of research projects designed to identify risk factors for stroke in minority populations and enhance prevention and treatment in these groups. The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study is an observational study to explore the role of race and geographic differences on stroke risk factor prevalence and stroke incidence and mortality. Recruitment of the main REGARDS cohort was completed at the end of 2007 with 30,229 participants (41 percent African American and 59 percent white, 55 percent female and 45 percent male), and includes participants from 1,833 of the 3,111 counties (59 percent) in the 48 contiguous United States. The group already has published a number of important findings that partially explain why African Americans and residents of the southeastern "Stroke Belt" have higher risk of dying from stroke, and also findings documenting the consequences of not reporting stroke symptoms, including poor health outcomes and death. NIH also has established an acute stroke research and care center at the Washington Hospital Center (WHC), a community hospital in Washington, DC, where more than 75 percent of stroke patients are African American or Hispanic. The center will collect data to aid in stroke prevention programs and will run two clinical trials, one on secondary stroke prevention and another on increasing tPA use among minorities. The program directly addresses GPRA goal: *By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities*.

→ Howard G, et al. *Prev Med* 2009;49(2-3):129-32. PMID: 19285103. PMCID: PMC2778033.
Cushman M, et al. *Ann Neurol* 2008;64(5):507-13. PMID: 19067365. PMCID: PMC2802965.
Howard G, et al. *Stroke* 2007;38(9):2446-52. PMID: 17673720.
Wadley, G, et al. *Stroke* 2007;38:1143-1147. PMID: 17322077.
→ For more information, see http://www.regardsstudy.org/index.htm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E, I) (**NINDS**) (GPRA)

The Sister Study: Environmental Risk Factors for Breast Cancer: The NIH Sister Study prospectively examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The frequency of relevant genes and shared risk factors is greater among sisters, increasing the ability of the study to detect risks. Researchers will collect data on potential risk factors and current health status, and will collect and bank blood, urine, and environmental samples for future use in studies of women who develop breast cancer or other diseases compared with those who do not. Analysis of new cases will assess the separate and combined effects of environmental exposures and genetic variations that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors like smoking, occupational exposures, alcohol, diet and obesity, and include analysis of phthalates, phytoestrogens, metals, insulin, growth factors, vitamins and nutrients, and genes in blood and urine. The study also allows investigators to examine a wide range of health outcomes of relevance to women, and to create a framework from which to test new hypotheses as they emerge. In addition to its focus on genetic and environmental causes of breast cancer, the prospective Sister Study tracks changes in health status over time. Among the chronic diseases currently studied are uterine fibroids and endometriosis, rheumatoid arthritis and other autoimmune diseases, thyroid disease, asthma, and cardiovascular diseases. As the cohort ages, the Sister Study will address aging-related health outcomes including osteoporosis, Parkinson's disease, and age-related cognitive decline.

→ For more information, see http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E/I) (**NIEHS**, NCMHD)

Advances in Minority Mental Health Research: Results from NIH's Collaborative Psychiatric Epidemiology Surveys (CPES) have continued to shed light on the risk, prevalence, and outcomes associated with mental disorders in minority populations. Two CPES surveys, the National Latino and Asian American Study (NLAAS), and the National Survey of American Life (NSAL), are large, nationally representative epidemiologic surveys that focus, respectively, on the mental health epidemiology of Latinos and Asians, and African Americans. Examples of important research that has emerged from the CPES include an FY 2009 study from the NSAL that found that African American teens, especially girls, are at increased risk for suicide attempts, even if they have not been diagnosed with a mental disorder. The study's findings may be used to improve clinicians' screenings for suicidal behavior among adolescent African Americans. Additionally, an FY 2009 study using data from the NLAAS and the National Co-morbidity Survey Replication found that previous research showing native-born Latinos to be at higher risk for mental disorders than nonnative-born Latinos may not be true across all Latino subgroups. NLAAS researchers found that this widely reported phenomenon (the “immigrant paradox”) was true in some subgroups, but it did not hold in others (e.g., among Puerto Ricans). The results emphasize the heterogeneity of the Latino population and suggest the importance of addressing this population's subgroups in future research.

→ Joe S, et al. *J Am Acad Child Adolesc Psychiatry* 2009;48(3):271-82. PMID: 19182692. PMCID: PMC2760075.
Alegria M, et al. *Am J Psychiatry* 2008;165(3):359-69. PMID: 18245178. PMCID: PMC2712949.
→ For more information, see http://www.nimh.nih.gov/science-news/2009/black-teens-especially-girls-at-high-risk-for-suicide-attempts.shtml
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIMH**)

A Look at Drug Abuse Trends: Local to International: Two major systems of data collection are helping to identify substance abuse trends locally, nationally, and internationally: Monitoring the Future Survey (MTF) and the Community Epidemiology Work Group (CEWG). Both help to surface emerging drug abuse trends among adolescents and other populations, and guide responsive national and global prevention efforts. The MTF project, begun in 1975, has many purposes, the primary one being to track trends in substance use, attitudes, and beliefs among adolescents and young adults. The survey findings also have been used by the President's Office of National Drug Control Policy to monitor progress toward national health goals. The MTF project includes both cross-sectional and longitudinal formats—the former given annually to 8th, 10th, and 12th graders to see how answers change over time, and the latter given every 2 years (until age 30), then every 5 years to follow up on a randomly selected sample from each senior class. CEWG, established in 1976, provides both national and international information about drug abuse trends through a network of researchers from different geographic areas. Regular meetings feature presentations on selected topics, as well as those offering international perspectives on drug abuse patterns and trends. CEWG findings reported in 2008 and 2009 show decreases in methamphetamine indicators (e.g., treatment admissions), suggesting that the problems that had escalated in the first half of the decade may have stabilized or declined. Development of a Latin American Epidemiology Network is underway. NIH also has provided technical consultation for the planning and establishment of an Asian multicity epidemiological network on drug abuse.

→ For more information, see http://www.monitoringthefuture.org/
→ For more information, see http://www.drugabuse.gov/about/organization/CEWG/CEWGHome.html
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E) (**NIDA**)

Fetal Alcohol Effects: The developing embryo and fetus is very vulnerable to the adverse effects of alcohol. Since Fetal Alcohol Syndrome was first recognized around 1970, NIH has supported research on outreach to pregnant women for identification and intervention of risky drinking; research to enhance our ability for early identification of and interventions with prenatal alcohol-affected children; research exploring nutritional and pharmacological agents that could lessen alcohol's adverse effects on the developing embryo/fetus; and research on how alcohol disrupts normal embryonic and fetal development. For example, a recent study with rats showed that choline, an essential nutrient, was found to effectively reduce the severity of some fetal alcohol effects, even when administered after the ethanol insult was complete. NIH also is investing in a large-scale prospective study looking at prenatal alcohol exposure along with other maternal risk factors in adverse pregnancy outcomes. Following a 3-year feasibility study, NIH established the Prenatal Alcohol, Sudden Infant Death Syndrome, and Stillbirth (PASS) Research Network, a multidisciplinary consortium to determine the role of prenatal alcohol exposure and other maternal risk factors in the incidence and etiology of sudden infant death syndrome (SIDS), stillbirth, and fetal alcohol syndrome, all of which are devastating pregnancy outcomes. The PASS study prospectively will follow 12,000 pregnant, high-risk, American Indian and South African women and their infants until the infants are 12 months old. Maternal, fetal, and infant measures and tissues will be obtained for analysis.

→ For more information, see http://www.nichd.nih.gov/research/supported/pass.cfm
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIAAA, NICHD**)

Improving the Lives of Asthmatic Children in the Inner City: The NIH Inner-City Asthma Consortium (ICAC) of 10 academic clinical centers, launched in 2002, evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. The Consortium also pursues studies to understand mechanisms underlying the onset and progression of asthma and research to develop diagnostic and prognostic biomarkers. An ICAC longitudinal birth cohort study involving 500 inner-city children is investigating the immunologic causes of the development of recurrent wheezing, which can be indicative of asthma in children under age 3. ICAC has extended the study to follow all participant children to age 7, when the diagnosis of asthma can be definitive. Researchers hope to identify immunologic characteristics that will predict the development and severity of asthma at a later age. ICAC researchers are conducting two clinical trials to determine the safety, dosing levels, and biologic activity of a potential new allergy immunotherapy for cockroach allergen, which ICAC studies previously found to be a major determinant of asthma severity among inner-city children. Finally, an ICAC clinical trial assessed the benefit of using exhaled nitric oxide (NO) as a marker for asthma management. Although the study reinforced the importance of the NIH asthma guidelines for disease control, it did not find that measuring exhaled NO provided any additional clinical benefit.

→ Szefler SJ, et al. *Lancet* 2008;372(9643):1065-72. PMID: 18805335. PMCID: PMC2610850.
→ For more information, see http://www3.niaid.nih.gov/topics/asthma/research/researchActivities.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAID**)

The Hispanic Community Health Study: In October 2006, NIH began the largest long-term epidemiological study of health and disease ever conducted in people of Hispanic/Latino heritage living in the United States. The study includes 16,000 participants of diverse Hispanic/Latino background, including Mexican, Cuban, Puerto Rican, and Central/South American. It is designed to identify factors that render these groups either susceptible to or protected from heart disease, stroke, asthma, chronic obstructive pulmonary disease, sleep disorders, dental disease, hearing loss, diabetes, kidney and liver disease, cognitive impairment, and other chronic conditions. Recruitment started in March 2008 in four cities. Variables such as height, weight, and other body measurements; blood pressure; blood lipids and glucose levels; diet; physical activity; smoking; acculturation; socioeconomic status; psychosocial factors; occupational history and exposure; access to and use of health care services; and use of medications and dietary supplements currently are being assessed.

→ For more information, see http://www.cscc.unc.edu/hchs
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NHLBI**, NCMHD, NIDCD, NIDCR, NIDDK, NINDS, ODP/ODS)

Outreach

Minority Health Information Access: An NIH outreach goal is to reduce health disparities among African American, Hispanic, and Native American populations by using a variety of approaches to promote access to and use of health information among diverse communities. The Historically Black Colleges and Universities (HBCU) ACCESS Project, developed in partnership with the United Negro College Fund Special Programs, provides technical assistance, training, and funding for locally developed projects incorporating the use of NIH information resources in HBCU campuses and communities. The Environmental Health Information Partnership enhances the capacity of 20 academic institutions that provide health-related services and information to health disparity populations by supporting their efforts to reduce health disparities through the access and use of environmental health information. Projects to increase the knowledge of Native Hawaiian community members about health information were completed at the community of Miloli'I and Waimanolo Health Center. At Cankdeska Cinkana Tribal College, Spirit Lake Nation, a health-related education program was developed along with tribal library improvements. Specialized websites, developed and expanded in partnership with community representatives, collect and organize information for specific populations such as Asian Americans, American Indians, and peoples of the Arctic. In the Lower Rio Grande Valley, the VIVA! Peer Tutors program at a magnet health high school is an award-winning effort to involve high school students in teaching their peers about online health information. The project has been extended to other schools and expanded to include promotion of health careers.

→ For more information, see http://sis.nlm.nih.gov/outreach.html
→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (I) (**NLM**)

MedlinePlus and MedlinePlus En Espanol: MedlinePlus and the Spanish language MedlinePlus En Espanol provide access to high-quality consumer health information on more than 800 diseases and conditions, with authoritative information from NIH, other government agencies, and health-related organizations. Enhancements in FYs 2008-2009 included improved search capabilities and addition of summary information. Content also was expanded to include information in more than 40 languages, addressing the growing needs of non-English-speaking patients. Go Local links from MedlinePlus, developed in partnership with libraries across the country, enable users to find relevant health services in local geographic areas. The number of Go Local sites increased to 34 in FY 2009, covering 46 percent of the U.S. population. The *NIH MedlinePlus Magazine* transmits the latest useful research findings in lay language, with feature stories on topics such as colorectal cancer, post-traumatic stress disorder, and childhood diseases. More than 600,000 copies of the magazine were distributed free to physician offices in FY 2009, up from 50,000 in FY 2006. In addition, a Spanish language edition, *Salud!*, was launched in FY 2009, as were online versions of both English and Spanish language magazines.

→ For more information, see http://www.medlineplus.gov
→ For more information, see http://medlineplus.gov/spanish
→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (I) (**NLM**)

National Network of Libraries of Medicine (NN/LM): With more than 5,800 full and affiliate members representing academic health sciences libraries, hospital libraries, public libraries, and community-based organizations, the NN/LM plays a pivotal role in NIH's outreach programs to reduce health disparities and improve health information literacy. In

FYs 2008-2009, NIH funded more than 400 community-based projects to enhance access to health information for health disparity and other medically underserved populations, building upon longstanding relationships with institutions providing health-related services and information to health disparity populations and developing many new relationships with schools, churches, public health departments, and others interested in improving health literacy and information access. Projects took place in rural and inner city communities and special populations in 35 states and the District of Columbia. The NN/LM also is a key player in the MedlinePlus "Go Local" service, which provides information about local community services to complement the nationally applicable health information in MedlinePlus. Go Local coverage reached 46 percent of the U.S. population in FYs 2008-2009. With an excellent track record of providing access to health information for clinicians and patients displaced by disasters, the NN/LM is the backbone of NIH's strategy to promote more effective use of libraries and librarians in local, State, and national disaster preparedness and response efforts. In FY 2008, a major initiative was the development of a national NN/LM Emergency Preparedness Plan to ensure backup health library services in the aftermath of a disaster and establish librarians as key community resources in disaster planning and response.

→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (E) (**NLM**)

Science Education Partnership Award (SEPA) Program: SEPA increases the public's understanding of medical research by: 1) increasing the pipeline of future scientists and clinicians, especially from underserved and rural kindergarten to grade 12 (K-12) students, and 2) engaging and educating the general public on health-related advances made possible by NIH-funded research. By creating relationships among educators, museum curators, and medical researchers, SEPA encourages the development of hands-on, inquiry-based curricula that inform subjects about timely issues, including obesity, diabetes, stem cells, and emerging infectious diseases. Additionally, SEPA projects are designed to enhance public trust by focusing on topics such as the clinical trials process, patient safeguards, and medical research ethics. Through SEPA exhibits at science centers and museums, the program provides educational and community outreach activities to tens of thousands of people every year. In FY 2008, SEPA supported 68 projects, of which 50 targeted middle- and high-school students and 18 were based in science centers and museums.

→ For more information, see http://www.ncrr.nih.gov
→ For more information, see http://www.ncrrsepa.org
→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (E) (**NCRR**)

Peer Tutor High School Program in the Lower Rio Grande Valley: The Peer Tutor Program is a school- and community-based collaborative outreach program that trains high school peer tutors in NIH online health information resources, and then empowers these students in turn to train their peers and to go into the local communities to train the citizenry. The majority of the peer tutors and students in participating schools are Hispanic. In place for more than 5 years, the program has trained more than 50 peer tutors who have conducted outreach to more than 2,500 high school students in the Lower Rio Grande Valley of Texas. Many peer tutors are active in the Health Occupations Student Association, and go on to succeed in college programs based in part on their peer tutoring experience. The program has grown from one high school at its inception, the South Texas High School for the Health Professions (known as MedHigh), to four high schools in the region, including a Science Magnet High School and a Health Technologies High School. The program successfully has engaged the Biblioteca Las Americas high school librarians with students, faculty, administrators, and community leaders to make a significant contribution to improving online health information access. The program includes curriculum development, co-teaching, and summer institutes within the schools, as well as health fairs and workshops in the local communities. The program has won several major awards, for example, from the Texas Library Association, National Commission on Libraries and Information Science, and Smithsonian Institute of Museum and Library Services.

→ For more information, see http://bla.stisd.net/viva.html
→ (E) (**NLM**)

Partnerships for Environmental Public Health: NIH is developing a unified program referred to as "Partnerships for Environmental Public Health" (PEPH). PEPH will support activities to build new partnerships with community groups/stakeholders, develop and/or disseminate educational and outreach materials, enhance communication with partners (i.e., town meetings, forums on selected topics), evaluate (process and outcome evaluations) strategies to quantify public health impact, or engage community and researchers in Environmental Health Science research projects. The purpose of this program is to provide support for grantees already working in this area to enhance current grant activities within the scope of the peer-reviewed application and to encourage scientists with a traditional research focus to communicate/translate their research into materials or messages that are useful to other groups, such as the lay public, health care professionals, decisionmakers, or educators. Building partnerships and translating research to communities is an important component in promoting health and preventing exposures that may have adverse human health effects. By building environmental health and science literacy, community residents are better prepared and equipped to take personal and community action to reduce exposures. Partnerships between researchers and community groups foster trust and lead to the identification of environmental health issues of concern to community residents, which may enhance the research results due to increased community participation.

→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (E) (**NIEHS**)

AIDS Information Services: NIH manages the HHS-wide AIDS*info* service, which offers the latest federally approved information on HIV/AIDS clinical research, treatment and prevention, and medical practice guidelines that are developed by working groups under the auspices of the OAR Advisory Council. An AIDS*info* trans-agency steering group spans NIH, FDA, HRSA, and CDC. *Info*SIDA, a Spanish-language version, features a customized home page and a search engine that locates Spanish-language resources within AIDS*info*. A new initiative to incorporate tens of thousands of abstracts from AIDS-related conferences held over the last decade into NIH's Web-based electronic information services also is underway, and testing for the first public release of the new data was conducted in FY 2009. In addition to providing information systems, NIH supports community outreach programs for underserved communities and special populations to promote improved access to HIV/AIDS information for health professionals, patients, the affected community, caregivers, and the general public. Emphasis is placed on supporting community-based organizations, libraries, faith-based organizations, and health departments to design and implement local programs that include information access topics related to information retrieval, skills development, Internet access, resource development, and document access, e.g., through collaboration with local public libraries. In FYs 2008-2009, NIH made 25 community outreach awards.

→ For more information, see http://aidsinfo.nih.gov
→ For more information, see http://aidsinfo.nih.gov/infoSIDA/
→ For more information, see http://sis.nlm.nih.gov/outreach/hiv_outreach.html
→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (I) (**NLM**)

Know Stroke Efforts and New Stroke Slogan: In 2004, NIH entered a partnership with CDC to launch a grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders who work as "Stroke Champions" to educate their communities about the signs and symptoms of stroke and the need for immediate action. The program focuses on reaching African Americans, Hispanics, and seniors in communities that have the health care systems in place to treat stroke. To date, the program has been implemented in 12 cities, educating 184 Stroke Champions who have conducted more than 600 community events. The program was

expanded this year to Charleston, South Carolina, and, as a follow-up to that program, materials will be developed for coastal communities with unique dialects. NIH also recently expanded its public education programs by collaborating with the Brain Attack Coalition (BAC) to develop a new action-oriented message that all member organizations could use with their current stroke awareness efforts. The BAC is a group of organizations committed to stroke prevention and treatment chaired by NINDS. The new slogan—"Stroke strikes fast. You should too. Call 9-1-1."—was launched in May 2009 during Stroke Awareness Month.

→ For more information, see http://stroke.nih.gov/about/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (O) (**NINDS**)

Disseminating Evidence-Based Health Information on Diabetes and Digestive and Kidney Diseases: The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational materials on diabetes and kidney disease, respectively. For example, the NDEP encourages people to take "small steps" to prevent type 2 diabetes. The NDEP also promotes the importance of comprehensive diabetes control in its "Control Your Diabetes. For Life" educational campaign. The NKDEP encourages African American families to discuss kidney disease at family reunions, and also provides tools and resources for health care providers to help coordinate care and improve patient outcomes for kidney disease. Both programs tailor materials for minority groups at high risk. Information Clearinghouses also provide key health information for patients, health care professionals, and the general public. A recent campaign highlighted the importance of using accurate methods to test hemoglobin A1c in people with diabetes who have sickle cell trait or other inherited hemoglobin variants. Other recent campaigns raised awareness of celiac disease and interstitial cystitis. The Weight-Control Information Network provides up-to-date, science-based information on weight control, obesity, physical activity, and related nutritional issues.

→ For more information, see http://www2.niddk.nih.gov/HealthEducation/
→ For more information, see http://ndep.nih.gov/
→ For more information, see http://nkdep.nih.gov/
→ For more information, see http://win.niddk.nih.gov/
→ This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (E) (**NIDDK**, CDC)

SIDS Outreach in Minority Communities: Since 1994, when NIH launched its campaign to reduce the risks of Sudden Infant Death Syndrome (SIDS), overall SIDS rates have declined significantly, yet the disparities continue to exist. Today, babies in the American Indian and Alaska Native communities are twice as likely to die from SIDS as white infants. To help eliminate this disparity, NIH, in collaboration with Native American Management Services, Inc., developed adaptable, culturally appropriate SIDS risk-reduction materials for use in five Indian Health Service Areas—Northern Tier-Aberdeen, Billings, Bemidji, Portland, and Alaska. Under the guidance of a community-based work group, educational materials have been developed based on recommendations from the five areas. The outreach project is called "Healthy Native Babies: Honoring the Past, Learning for the Future." Project materials include a training manual and a CD-ROM. The interactive CD-ROM that has been developed includes templates for a variety of SIDS risk-reduction educational materials. It contains photographs of American Indian and Alaska Native families and infants from the five regions, taken by local photographers. These photographs can be incorporated into educational materials such as posters, flyers, brochures, and postcards.

→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (O) (**NICHD**)

Providing Science-Based Oral Health Information: NIH provides science-based oral health information tailored to meet specific needs. Two examples are described here.

- *Practical Oral Care for People with Developmental Disabilities:* Finding dental care in the community is challenging for people with developmental disabilities. Many dentists do not feel trained sufficiently to provide services to people with special needs. To help increase access to dental care, NIH developed a series of publications to equip general dentists with information they need to deliver quality oral care to persons with developmental disabilities. The series includes continuing education (CE) programs for dentists and dental hygienists and a guide for caregivers describing their important role in maintaining good oral health for their family member or client. The modules are so popular that NIH has extended the CE credit through 2011.
- *Spanish-Language Oral Health Website:* The Special Care Dentistry Association partners with NIH in this important health education outreach—Spanish-Language Oral Health Website. This new Spanish-language website tailored for U.S. Hispanics/Latinos increases Spanish speakers' access to science-based oral health information. The site recently was tested in two cities; participants were Spanish-dominant and bilingual Latinos with backgrounds from different countries of origin and with varying levels of education. The test was to ensure the new website is understandable, credible, and attractive to the intended audience. Other goals included understanding the approach Latinos take when seeking health information online, what they think of the quality of online health information, and whether there are significant differences between Spanish-dominant and bilingual individuals.

→ For more information, see http://www.nidcr.nih.gov/OralHealth/Topics/DevelopmentalDisabilities/
→ For more information, see http://www.nidcr.nih.gov/espanol
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (O) (**NIDCR**, NICHD)

Collaboration with National Coalition of Ethnic Minority Nurse Associations (NCEMNA): NIH conducts outreach activities focused on health disparities research through its relationship with NCEMNA. Comprised of five ethnic nurse associations, NCEMNA strives to increase the number of minority nurses in the United States and increase the amount of minority health-related research. Over the past several years, NIH has provided informational materials to NCEMNA member associations to increase awareness of NIH research opportunities for underserved investigators. In addition, NIH has participated in workshops with NCEMNA members at which NINR senior leadership has presented information about the Institute, and NINR program directors have met individually with prospective investigators and trainees.

→ (E) (**NINR**, NIGMS)

Research/Outreach

Collaborative Community-Based Research: NIH is focusing on strategies and best practices for conducting collaborative community-based clinical and translational research, particularly in minority and other medically underserved communities where health disparities persist. Programs such as the Institutional Development Award (IDeA) are encouraging efforts to build and strengthen partnerships among government agencies, academic and private-sector organizations, community health providers, and organizations that also are working to improve community health outcomes. Translational, community-based research funded in several IDeA states, in both urban and rural settings, is focusing on:

- Enhancing recruitment and retention of research subjects through community buy-in
- Implementing practical and effective research protocols in community health care settings
- Developing versatile and sustainable core research infrastructure to encourage community participation and leverage existing resources

In addition, in FYs 2008 and 2009, NIH conducted workshops to gather specific recommendations from the community that are helping to shape future initiatives to enhance clinical and translational research in minority and other medically underserved communities. Workshop participants included other HHS-agencies such as AHRQ, CDC, the Indian Health Service, and HRSA.

→ For more information, see http://www.ncrr.nih.gov/research_infrastructure
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**)

Community Participation in Health Disparities Intervention Research Program: NIH supports the development, implementation, and evaluation of intervention research by using community-based participatory research (CBPR) principles and methods in targeting diseases of major public health importance in health disparity communities. This unique multiyear CBPR initiative promotes participatory research collaborations between scientific researchers and their community partners and will engage communities in all stages of the research process for a total of 11 years (3-year planning phase, 5-year intervention phase, and 3-year dissemination phase). The participatory partnerships formed between researchers and the community are expected to (1) transform the research questions from researcher to community-centered; (2) focus the research area, strategies, and methods to address those diseases and conditions of highest community interest and need; and (3) accelerate the identification and testing of interventions that are likely to make the largest difference in the health of the community. The CBPR initiative began in FY 2005 with the award of 25 3-year research planning grants. CBPR planning grantees conducted needs assessments, focus groups, and pilot intervention studies for addressing health disparities among health disparity populations in 20 states. In FY 2008, 40 5-year intervention research grants focusing on diabetes, cancer, cardiovascular disease, substance abuse, and other diseases and conditions were awarded. This intervention phase will be followed by a competition for 3-year dissemination grants to be awarded in FY 2013. In May 2009, RFA MD-09-006, "Recovery Act Limited Competition: NCMHD Community Participation in Health Disparities Intervention Research Planning Phase," was issued for a 2-year planning research phase. Awards for this phase were made in FY 2009. Current CBPR pilot intervention research studies include:

- Suicide and alcohol use prevention among Alaska Native youth living in five communities in Alaska
- HIV/AIDS prevention among African Americans in North Carolina
- Obesity prevention using individual, family, and community-level interventions among Native Hawaiian and Pacific Islanders in Hawaii
- Diabetes prevention among Hispanic communities in border areas in Texas
- Hypertension prevention among Filipino Americans in New York City and New Jersey
- Cancer prevention among low-income Appalachian communities in Ohio by increasing colorectal cancer screening

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/rfa-md-07-003.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-09-006.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NCMHD**)

Community-Based Participatory Research (CBPR): CBPR is an orientation to research that requires a collaborative approach to involve community stakeholders throughout all stages of research projects. This community input offers CBPR the potential to generate better-informed hypotheses, develop more effective interventions, and enhance the translation of research results into practice. NIH issued three funding opportunity announcements (FOAs) on CBPR in January 2008. One FOA, Community Participation in Research, solicits jointly conducted intervention research. The remaining FOAs, Community Participation Research Targeting the Medically Underserved, solicit jointly conducted research in medically underserved areas/populations; all three FOAs focus on health promotion, disease prevention, and health disparities. A corresponding technical assistance workshop, Leap into the Community, convened February 2008 and

offered comprehensive instruction from NIH program and review officials on the CBPR approach and preparing responsive applications to the FOAs. Outreach and training activities on CBPR have included the creation of an educational brochure (November 2007); organization of two special sessions at annual scientific meetings for the Society of Behavioral Medicine and the American Sociological Association on the principles and efficacy of CBPR and showcasing successful NIH-funded research projects (March 2008 and August 2009, respectively); and planning of the 2009 NIH Summer Institute on Community-Based Participatory Research Targeting the Medically Underserved, which addresses essential issues inherent in conducting community-partnered research with medically underserved areas/populations (August 2009).

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-074.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-075.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-076.html
→ For more information, see http://obssr.od.nih.gov/scientific_areas/methodology/community_based_participatory_research/CBPR_TA_Wrkshp.aspx
→ For more information, see http://obssr.od.nih.gov/scientific_areas/methodology/community_based_participatory_research/CBPR_ASA.aspx
→ For more information, see http://conferences.thehillgroup.com/si2009/index.html
→ For more information, see http://obssr.od.nih.gov/scientific_areas/methodology/community_based_participatory_research/index.aspx
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**OBSSR**, CDC/NIOSH, NCI, NHLBI, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINR, ORWH)

Research Partnerships: Fostering partnerships is a key component of the multifaceted NIH strategic approach to eliminating health disparities. NCMHD funds a broad range of collaborations with the other NIH ICs and other Federal agencies. NCMHD co-funded projects leverage the existing strengths, resources, and research potential of key Federal research partners. Since 2001, NCMHD has devoted more than $300 million to support several hundred research, training, community outreach, and capacity-building projects. Examples include:

- *The Jackson Heart Study* (with NHLBI) is a population-based longitudinal cohort study of African Americans examining genetic, biological, and environmental risk factors for the development and progression of cardiovascular disease. The study is the largest single-site, prospective, epidemiologic investigation of cardiovascular disease among African Americans ever undertaken. Currently, follow-up data collection is ongoing to include 4000 CT scans by December 2009.
- *The Sister Study* (with NIEHS), is a national study investigating environmental and genetic breast cancer risk factors. The Sister Study is the only long-term study in the United States and Puerto Rico of women aged 35 to 74 whose sisters had breast cancer. Begun in 2003, the study is prospectively examining the environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer.
- *The Navajo Bone Health Study* (with NIAMS) is focusing on the surveillance of bone health in the Navajo Nation. These efforts in time will enable the Navajo Nation to plan screening and culturally appropriate education and intervention programs targeted toward the segments of the population at greatest risk for fracture or osteoporosis.
- *Racial and Ethnic Approaches to Community Health Across the U.S.* (REACH U.S.) is a CDC program promoting community coalitions that design, implement, evaluate, and disseminate community-driven strategies to eliminate health disparities in key health areas. In FY 2009 NIH supported a REACH US initiative with Morehouse School of Medicine and its partners to increase breast and cervical cancer screening among African American women in North Carolina and South Carolina. Also, NIH funding to Virginia Commonwealth University promoted prenatal care in African American women in Virginia.

- *Interventions for a Focused Diabetes and Chronic Kidney Disease (CKD) Disparities Project* is a CMS initiative improving the quality of care for Medicare beneficiaries through interventions that will improve diabetes measures and detect the incidence, decrease the progression, and improve care of those with CKD, in a targeted underserved population. NCMHD funding has been supporting the development of intervention research projects within the Mississippi Delta Region.

  → (E) (**NCMHD**, CDC, CMS, NHLBI, NIAMS, NIEHS)

Getting Proven Treatments into the Criminal Justice System: Unfortunately, most inmates in need of substance abuse treatment do not receive it while in prison and, upon their release, continue a vicious cycle of drug use and crime. In response, NIH—along with multiple Federal agencies and health and social service professionals—is working systematically to move science-based treatment interventions into the criminal justice system, where they can have a major impact. In a Delaware Work Release study, those who participated in prison-based treatment followed by aftercare were 7 times more likely to be drug free after 3 years than those who received no treatment. Other research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) affirms the critical need for prisoners to receive effective substance abuse treatment while incarcerated and during their re-entry into the community. A recent randomized clinical trial found that prisoners who began methadone maintenance treatment in prison were significantly more likely after 12 months post-release to continue treatment and decrease drug use and criminal activity than a counseling-only group. A related issue for this population is heightened HIV risk—the U.S. prison system also being where many inmates first receive HIV testing and initiate treatment. However, only a nominal percentage continues this treatment following release. New research shows that simply providing formal assistance in filing the paperwork for antiretroviral treatment medications can promote greater continuity of HIV pharmacotherapy among released inmates. Gaining insight into ways to reduce drug use and criminal recidivism—including among adolescents for whom the same issues apply—as well as limit HIV spread in communities means huge economic and social cost savings.

→ Baillargeon J, et al. *JAMA* 2009;301(8):848-57. PMID: 19244192.
Chandler RK, et al. *JAMA* 2009;301(2):183-90. PMID: 19141766. PMCID: PMC2681083.
Kinlock TW, et al. *J Subst Abuse Treat* 2009;37(3):277-85. PMID: 19339140. PMCID: PMC2803487.
Martin SS, et al. *Prison J* 1999;79(3):294-320.
→ For more information, see http://www.cjdats.org/
→ For more information, see http://www.drugabuse.gov/Blending/
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDA**) (GPRA)

Rural Latino Preschooler's Oral Health: Intersections among Family, Community, Providers and Regulators: Latino children experience among the highest prevalence of early childhood dental caries in the United States. Researchers explored the intersections among four societal sectors or contexts of care that potentially contribute to oral health disparities for low-income, preschool Latino children in rural California. The ethnographic investigation was conducted in a predominately Mexican-American agricultural community. Observations occurred in homes, community facilities, and dental offices, and were supplemented with in-depth interviews by trained anthropologists with key community informants and primary caregivers of children less than 6 years old. Factors that significantly intersected to produce or sustain poor oral health care for children follow. Caregivers did not always recognize signs of decay among their children, nor quickly respond unless children also complained of pain. Fluctuating eligibility for health insurance intersected with limited community infrastructure and civic amenities, including lack of public transportation, to create difficulties in access to care. Nonfluoridated bottled water often was consumed rather than tap water because of fears about potential pesticide pollution of the municipal water supply. Multiple dental visits caused parental hardship and occasionally resulted in the loss of the caregiver's job. Dental fear and poor provider-caregiver communication were exacerbated by a scarcity of dentists willing to serve rural low-income populations. Such empirical research related to

newly emerging conceptual models is greatly needed. Understanding that multiple, intersecting factors at numerous levels will inform intervention research customized to the individual, community, and society.

→ Barker JC, Horton SB. *BMC Oral Health* 2008;8:8. PMID: 18377660. PMCID: PMC2362117.
→ For more information, see http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/DentalCaries/DentalCariesChildren2to11
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDCR**)

Understanding and Promoting Health Literacy: Low health literacy is a widespread problem, affecting more than 90 million adults in the United States, where 43 percent of adults demonstrate only the most basic or below-basic levels of prose literacy. Low health literacy results in patients' inadequate engagement in decisions regarding their health care and can hinder their ability to realize the benefits of health care advances. Research has linked low or limited health literacy with such adverse outcomes as poorer self-management of chronic diseases, fewer healthy behaviors, higher rates of hospitalizations, and overall poorer health outcomes. An NIH program announcement supports research that increases our understanding of the health literacy problem and its relationship to health disparities as well as the development of interventions to overcome the adverse consequences of low health literacy. In December 2008, a grantee meeting was convened to provide a venue for NIH-funded scientists conducting health literacy research to discuss lessons learned about health literacy-related topics, including measurement and methodology, actionable research (e.g., plain language, dissemination), and special populations (e.g., cognition, culture, and socioeconomic status). NIH is planning a fall workshop to highlight the state-of-the-science and to inform directions for reissuing the funding opportunity announcement in 2010.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-020.html
→ For more information, see http://obssr.od.nih.gov/scientific_areas/social_culture_factors_in_health/health_literacy/index.aspx
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**OBSSR**, AHRQ, NCI, NHLBI, NIA, NIBIB, NICHD, NIDCD, NIDCR, NIEHS, NIMH, NINR, NLM)

Research Training

Minority Health and Health Disparities International Research Training (MHIRT) Program: In 2009, NIH provided funding for the MHIRT Program, which allowed 22 academic institutions to administer international training opportunities in health disparities research for more than 150 undergraduate and graduate students. The current funding cycle builds on the success of previous MHIRT Program activities and contributes to the elimination of health disparities in the United States by developing a cadre of health disparities researchers with international experience. Many MHIRT subjects are engaged in research that investigates the use of biomedical processes in eliminating health disparities, genetics, pharmaco-dynamic trends, socioeconomic, behavioral, psychosocial, and other fundamental determinants of health disparities. The trainees are placed worldwide at foreign collaborating sites in Argentina, Australia, Botswana, Brazil, Chile, China, Czech Republic, Dominican Republic, Ecuador, England, Ethiopia, Finland, France, Germany, Ghana, Guatemala, India, Italy, Jamaica, Japan, Mexico, New Zealand, Peru, Poland, Republic of Georgia, Romania, Slovak Republic, South Africa, South Korea, Spain, Swaziland, Sweden, Thailand, Uganda, and Vietnam. African American and Hispanic undergraduate and graduate students constitute the largest racial and ethnic groups participating in MHIRT training programs.

→ (E) (**NCMHD**)

NIH Research Supplements to Promote Diversity in Health-Related Research: These supplements have broad eligibility criteria designed to support and recruit students, postdoctorates, and eligible investigators from diverse backgrounds underrepresented in the biomedical, behavioral, and clinical and social sciences research workforce. The

program specifically seeks to recruit and retain individuals from diverse backgrounds underrepresented in biomedical research, including (1) individuals from racial and ethnic groups shown by the National Science Foundation to be underrepresented in the health-related sciences, (2) individuals with disabilities, and (3) individuals from disadvantaged backgrounds. NIH expects efforts to diversify the workforce to lead to (1) the recruitment of the most talented researchers from all groups, (2) an improvement in the quality of the educational and training environment, (3) a balanced perspective in the determination of research priorities, (4) an improved capacity to recruit subjects from diverse backgrounds into clinical research protocols, and (5) an improved capacity to address and eliminate health disparities. NIH believes that diversity in the biomedical, behavioral, clinical, and social sciences research workforce will bring a more balanced perspective to the determination of research priorities, increased diversity in clinical trials, and a new synergy to the study of health disparities.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-190.html
→ (E) (**NCMHD**)

Resource Centers for Minority Aging Research (RCMARs): Since 1997, RCMARs have provided a venue for increasing the number of researchers who focus on the health of older minority adults, enhancing diversity in the professional workforce, improving recruitment and retention of minority older adults in research studies, and creating culturally sensitive health measures that assess the health status of minority older adults with greater precision and increase the effectiveness of interventions designed to improve their health and well-being. As of 2006 (the most recent year for which data are available), 197 RCMAR scholars from diverse backgrounds had been funded across 6 sites. A recent independent evaluation of the RCMARs found that 74 percent of the scholars between 1997 and 2005 had published at least 1 article in a peer-reviewed journal after joining a RCMAR, and 57 percent were first authors. Whereas only 13 percent of RCMAR participants had received a Public Health Service grant prior to joining the program, 28 percent received 1 or more after joining the program. RCMAR scholars and affiliated faculty have published 78 scholarly articles and 2 special issues of journals on recruitment and retention of minority elders in clinical trials, and have developed an active website on measurement, conducted 2 conferences on this topic, and published many articles relating to the development of culturally sensitive measures of health status.

→ For more information, see http://www.rcmar.ucla.edu
→ (E) (**NIA**)

Loan Repayment Program for Health Disparities Research: To promote a diverse and strong scientific workforce effectively, it is necessary to expand and create transitioning and financial aid programs, which help alleviate barriers that discourage many students from pursuing a research career. The Loan Repayment Program for Health Disparities Research (LRP) is designed to increase the number of highly qualified health professionals in research careers focused on health disparities. Pursuant to Pub. L. No. 106-525, at least 50 percent of the awards will be made to individuals from health disparity populations. The Extramural Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds (ECR-LRP) seeks to increase the participation of highly qualified health professionals from disadvantaged backgrounds in clinical research careers. To develop synergies between the programs and ensure that emphasis is placed on minority health and other health disparities research efforts, NIH will work to establish links between the MHIRT program, LRPs (LRP and ECR-LRP), and NIH research priorities. In 2009, NIH made awards to 314 participants.

→ (E) (**NCMHD**)

Collaborations Between Minority-Serving Institutions and Cancer Centers: The Minority Institution (MI)/Cancer Center (CC) Partnership (MI/CCP) is a flagship program that has been instrumental in establishing strong collaborations between minority-serving institutions (MSIs) and CCs. MI/CCP has fostered strong cancer research partnerships throughout the United States. This program established new cancer research curricula, recruited new faculty, increased awareness about health care disparities and cultural sensitivities, and developed programs and outreach efforts in educating underserved communities. The MI/CCP has provided research education and training to individuals at all levels including postdoctoral fellows, medical students, graduate students, students at master's level, and baccalaureate and high school students. Establishing new collaborations and partnerships in communities has been a hallmark of this program, culminating in increases in numbers of awarded grant applications and numbers of manuscripts, oral presentations, and poster presentations at both regional and national levels. Many research advances are emerging from the Partnership. For example, through the Morehouse School of Medicine and University of Alabama Partnership, researchers have identified a possible genetic cause for increased risk for a more advanced form of colorectal cancer in blacks that leads to shorter survival. Understanding the relationship between molecular defects and differences in colorectal cancer incidence, aggressiveness, and clinical outcomes is important in individualizing the treatment and in eliminating racial disparities.

→ For more information, see http://crchd.cancer.gov/research/miccp-overview.html
→ For more information, see http://clincancerres.aacrjournals.org/cgi/content/full/15/7/2406
→ This example also appears in Chapter 2: *Cancer*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCI**)

Research Capacity

Expanding NIH's Capacity to Conduct Minority Health and Health Disparities Research:

- *Health Disparities Research on Minority and Underserved Populations (R01) Program*: NIH established this program in FY 2009 to implement the science, practice, and policy paradigm and enhance its focus on building the science and health professions workforce for health disparities. It provides an additional means for supporting innovative research projects. A total of eight awards were made in FY 2009.
- *NCMHD Intramural Research Program*: The NCMHD Intramural Research Program (IRP) was approved in FY 2009. An on-campus program, the IRP will: (1) conduct state-of-the-art research focusing on the linkage between biological and nonbiological determinants of health in health disparity populations; (2) create training and mentorship opportunities; and (3) contribute to the diversity of early-stage and seasoned investigators at NIH.
- *Disparities Research and Education Advancing our Mission (DREAM) Program*: Launched in FY 2009, this career development program aims to retain promising investigators in health disparities research careers, including those who have successfully completed the Loan Repayment Program for Health Disparities Research.
- *American Recovery and Reinvestment Act (ARRA)*: Under ARRA, the NCMHD has developed significant new health disparities research and research capacity-building opportunities. The NCMHD "*Grand Opportunities"* grants support high-impact ideas that lend themselves to short-term funding and may lay the foundation for new fields of investigation. Challenge grants address specific knowledge gaps, scientific opportunities, new technologies, data generation, or research methods. The Grand Opportunities and Challenges grants support: clinical research efforts, comparative effectiveness research examining approaches that address access barriers, wireless technologies research, research on ethical issues and health disparities, and other research on health disparities factors. Other initiatives established under ARRA include a Dissertation Research Award.

→ (I) (**NCMHD**)

Research Endowment Program: The NCMHD Research Endowment Program specifically targets "Section 736 [Public Health Service Act] Institutions with currently funded Programs of Excellence in Health Professions Education for Underrepresented Minority Individuals." Congress mandated the creation of this unique program in the legislation that

created the NCMHD (Pub. L. No. 106-525). This program makes significant investments in the education and training of individuals from diverse backgrounds, including racial/ethnic minority and other individuals from health disparity populations who are underrepresented in the scientific workforce. NCMHD-endowed institutions are using endowment funds to enhance research capacity and infrastructure for research and training by strengthening teaching programs in the biomedical and behavioral sciences and related areas; making physical plant improvements; establishing endowed chairs and programs; obtaining equipment for instruction and research; enhancing student recruitment and retention; providing merit-based scholarships; recruiting and retaining faculty and developing instruction delivery systems and information technology, in areas that enhance minority health and health disparities research activities; and training minority and disadvantaged scientists in the behavioral and biomedical sciences.

→ (E) (**NCMHD**)

Research Infrastructure in Minority Institutions (RIMI) Program: (Note: The RIMI program will be replaced by the Building Research Infrastructure and Capacity [BRIC] program in FY 2010.) The RIMI program establishes and improves the scientific infrastructure at nonresearch intensive academic institutions. RIMI provides resources to strengthen faculty-initiated research programs, enhance academic development of students in science and mathematics, and improve the capacity for training future research scientists.

The RIMI program supports building research capacity in 2-year colleges and other nonresearch intensive academic institutions that only offer associate's degrees, baccalaureate, and/or master's degrees in the basic, life, behavioral, or social sciences. The RIMI program enables an institution to:

- Strengthen its basic research infrastructure and the institution's science programs;
- Institute a comprehensive faculty development research training program;
- Establish an academic career development training program for students interested in pursuing a career in the biomedical sciences; and
- Support individual faculty-initiated research projects that may lead to the development of independent researchers in minority health and health disparities.

The RIMI program helps nondoctoral degree-granting institutions develop and enhance their research infrastructure and their capacity and competitiveness to conduct biomedical, clinical, and/or behavioral research.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-08-002.html
→ (E) (**NCMHD**)

Research Centers in Minority Institutions (RCMI): The RCMI program has developed and enhanced the research infrastructure of minority-serving institutions by expanding human and physical resources for conducting basic, clinical, and translational research. It began in 1985 in response to congressional report language (House Report 98-911, on the Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill for FY 1985; July 26, 1984; pages 78-79), directing funds to “establish research centers in those predominantly minority institutions which offer doctoral degrees in the health professions or the sciences related to health.” The RCMI program has provided resources to acquire advanced instrumentation, renovate laboratory facilities, and improve research infrastructure. Additionally, it has enhanced faculty development, funded pilot projects, and supported core facilities. Because many RCMI investigators study diseases that disproportionately affect minorities, NIH support has brought more minority scientists into mainstream research and enhanced biomedical research focused on improving the health of racial and ethnic minorities and other medically underserved populations. The RCMI program includes various types of awards to help improve research capacity and reduce health disparities. For example, the RCMI Translational Research Network has fostered collaboration among researchers, developed and shared practices in disease prevention in local communities, and funded informatics

tools for managing clinical research data. The RCMI program also has supported Clinical Research Education and Career Development awards that provide didactic training and mentor clinical research experiences to develop independent researchers.

→ For more information, see http://www.ncrr.nih.gov/ircmi
→ For more information, see http://www.ncrr.nih.gov/rtrn
→ For more information, see http://www.ncrr.nih.gov/crecd
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**, NCMHD, NHLBI, NIA, NIAMS, NICHD, NIDA, NIDDK, NIMH)

Institutional Development Award (IDeA) Program: The NIH IDeA program fosters health-related research and improves the competitiveness of investigators in 23 states and Puerto Rico with historically low NIH funding. The IDeA program supports multidisciplinary centers and statewide collaborative partnerships that increase institutions' capacity to conduct cutting-edge biomedical research. IDeA supports faculty development and enhancement of research infrastructure at institutions and also promotes collaborative community-based research, particularly in minority communities and other medically underserved communities where health disparities persist. The IDeA program supports the IDeANet initiative, which is expanding access to high-performance computational resources for data-intensive science applications and providing bioinformatics software tools and training to investigators. IDeANet began with the Lariat Networking Project, a pilot program that has enabled connectivity in six IDeA states in the Northwest (Alaska, Hawaii, Idaho, Montana, Nevada, and Wyoming) in partnership with the University of Washington and the University of California, San Diego. The Louisiana Optical Network Initiative (LONI) followed, supporting high bandwidth connectivity in Louisiana and Mississippi. Recently, five IDeA states have formed the North East Cyberinfrastructure Consortium (Delaware, Maine, New Hampshire, Rhode Island, and Vermont). IDeANet ultimately will enable all institutions in the IDeA program to engage in national and international collaborations.

→ For more information, see http://www.ncrr.nih.gov/riidea
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**) (GPRA)

Clinical and Translational Science Award (CTSA) Program Progress: Launched in 2006, NIH has made significant progress in building a national consortium for clinical and translational research. Since 2008, 22 new CTSAs joined the consortium, adding representation from eight new states, additional pediatric expertise, and greater informatics capabilities. At the national level, the CTSA consortium has identified five strategic goals: developing strategies and resources to move laboratory discoveries into early clinical testing (T1 translation), reducing complexities and improving ways clinical and translational research is conducted, enhancing training and career development of clinical and translational investigators, encouraging consortium-wide collaborations, and improving the health of communities across the nation—with an emphasis on community engagement and comparative effectiveness research. Working together, the consortium has made substantial progress in improving the management of clinical research, developing core competencies in clinical and translational science, and accelerating the dissemination of research findings into clinical practice. The momentum of the CTSA consortium continues to build as new connections are emerging rapidly within, across, and beyond the consortium. For example, CTSAs are connecting with the following NIH-funded institutions: Emory University (Atlanta, Georgia) is partnering with Morehouse School of Medicine; Vanderbilt University (Nashville, Tennessee) is partnering with Meharry Medical College; and Weill Cornell Medical College (New York, New York) is partnering with Hunter College.

→ For more information, see ht tp://www.ncrr.nih.gov
→ For more information, see http://www.ctsaweb.org
→ For more information, see http://www.ncrr.nih.gov/ctsa/progress_report_2009

→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**, Common Fund - all ICs participate)

ARRA-Funding Expands Research Capabilities: NCRR is using its ARRA funds designated for scientific research to accelerate the Center's research priorities and support research, resources, tools, and training to help researchers funded by NIH transform basic discoveries into improved human health. In contrast to most of the NIH ICs that fund primarily Research Project Grants (i.e., R01s), NCRR primarily supports large Center programs that build research capacity and offer training and career development. Consistent with NCRR's research portfolio, a few previously reviewed Research Project Grants (R01s and R21s) are being awarded with ARRA funds. Through competitive revision awards, NCRR is encouraging NIH-funded researchers (primarily supported by other NIH ICs) to leverage the resources, expertise, and infrastructure of NCRR centers and Center-like programs. To further advance the scientific progress of NCRR programs, administrative supplements are being awarded to: advance translational (pre- and post-clinical) research, achieve CTSA consortium strategic goals, enhance NCRR pilot project mechanisms, promote collaborative community engagement research, improve research workforce development, and strengthen science education and dissemination. A new ARRA-supported initiative will develop infrastructure to connect people and resources across the Nation and promote interdisciplinary collaborations and scientific exchange. Additional ARRA funding is supporting NIH-led activities such as the Challenge Grants and the Summer Research Experiences for Students and Science Educators. From the beginning of the ARRA-funding strategy development, NCRR leadership decided to align its ARRA activities broadly with the goals and objectives of the NCRR 2009-2013 Strategic Plan.

→ For more information, see http://www.ncrr.nih.gov/recovery
→ For more information, see http://www.ncrr.nih.gov/strategic_plan/implementation/
→ This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
→ (E) (**NCRR**) (ARRA)

NIH Strategic Plans Pertaining to Minority Health and Health Disparities Research

NIH-Wide Strategic Plan

- *NIH Health Disparities Strategic Plan, Fiscal Years 2004-2008*

The NIH Health Disparities Strategic Plan, Fiscal Years 2009-2013 is being developed. The NIH Health Disparities Strategic Plan Working Group, comprised of eminent leaders in minority health and health disparities research, has been convened by the NCMHD Director to guide the development of this new plan. Upon completion, the new plan will be posted to RePORT.

Note: Every IC has a Strategic Plan on Health Disparities. These plans are contained with the NIH plan. Nonetheless, because several ICs also separately publish those plans and others that address defined populations that are subject to health disparities, we are listing these separately published plans here.

Office of AIDS Research (OAR)

- *FY 2008 Trans-NIH Plan for HIV-Related Research*
- *FY 2009 Trans-NIH Plan for HIV-Related Research*
- *FY 2010 Trans-NIH Plan for HIV-Related Research*

National Institute of Allergy and Infectious Diseases (NIAID)

- *Women's Health in the U.S.: Research on Health Issues Affecting Women (2004)*

National Institute on Drug Abuse (NIDA)

- *NIDA Five-Year Strategic Plan 2009*
- *Strategic Plan on Reducing Health Disparities*

National Institute of Dental and Craniofacial Research (NIDCR)

- NIDCR Strategic Plan
- NIDCR Implementation Plan

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

- *Strategic Plan on Minority Health Disparities*

National Institute of Environmental Health Sciences (NIEHS)

- Worker Education and Training Program (WTEP) Strategic Plan 2008-2013

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Estimates of Funding for Various Research, Condition, and Disease Categories

The table below provides insight into NIH research funding on the topics addressed in this chapter and is abstracted from the most recent version of NIH's Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC). That publicly available source table displays information that NIH routinely collects on agency-wide funding in areas of special interest. In each such area, the table below indicates whether some of the funding pertains to the topics in this chapter.

Important Notes

- NIH does not expressly budget by category. The annual figures reflect amounts that change as a result of science, actual research projects funded, and the NIH budget.
- The FY 2008 and FY 2009 funding levels are based on actual grants, contracts, intramural research, and other mechanisms of support.
- FY 2009 data is differentiated by funding source, i.e., non-ARRA (regular appropriations) and ARRA (Recovery Act).
- The research categories are not mutually exclusive. Because individual research projects can be included in multiple categories, amounts depicted within each column of this table do not add up to 100 percent. For example, Clinical Research includes Clinical Trials. Also, Fragile X Syndrome, Genetics, and Intellectual Disability each overlap to some extent, as do Topical Microbicides, HIV/AIDS, and Prevention.
- For most of the areas listed, only a portion of the funding pertains to the indicated topic. For example, only a portion of NIH funding on Agent Orange and Dioxin pertains to Neuroscience and Disorders of the Nervous System, but because a fraction does, that area is checked.

Table 2-1: Estimates of Funding For Various Research, Condition, and Disease Categories

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Acute Respiratory Distress Syndrome	82	103	17			X				
Agent Orange & Dioxin	13	13	2		X					

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Aging	1,965	3,015	554	X	X	X		X	X	X
Alcoholism	452	441	75	X	X	X		X	X	X
Allergic Rhinitis (Hay Fever)	6	4	1				X			
ALS	43	43	13		X					
Alzheimer's Disease	412	457	77		X				X	
American Indians/Alaska Natives	142	169	19	X	X	X		X		X
Anorexia	7	8	2		X				X	
Anthrax	134	102	13			X				
Antimicrobial Resistance	228	251	52			X				
Aphasia	22	22	3		X					
Arctic	22	28	6			X	X			
Arthritis	232	246	65		X	X	X	X	X	X
Assistive Technology	215	249	43		X			X	X	

Estimates of Funding for Various Research, Condition, and Disease Categories

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Asthma	246	284	51				X	X		X
Ataxia Telangiectasia	13	13	2		X					
Atherosclerosis	460	495	112		X	X		X		
Attention Deficit Disorder (ADD)	60	71	13		X			X	X	
Autism	118	132	64		X				X	
Autoimmune Disease	762	879	138		X		X			X
Basic Behavioral and Social Science	1,149	1,410	206	X	X	X	X	X	X	X
Batten Disease	5	5	2		X					
Behavioral and Social Science	3,215	3,471	582	X	X	X	X	X	X	X
Biodefense [203]	1.736	1,746	213		X	X				
Bioengineering	2,853	3,155	569	X	X	X	X	X	X	
Biotechnology	5,179	5,619	1,051	X	X	X	X	X	X	X
Brain Cancer	194	234	42	X	X					
Brain Disorders	3,729	3,538	685		X	X	X			

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Breast Cancer	726	722	111	X					X	X
Cancer	5,570	5,629	1,120	X	X	X	X		X	X
Cardiovascular	2,027	2,008	396	X	X			X	X	X
Cerebral Palsy	28	21	4		X				X	
Cervical Cancer	69	84	15	X						X
Charcot-Marie-Tooth Disease	12	14	2		X					
Child Abuse and Neglect Research	30	32	5		X				X	
Childhood Leukemia	39	47	12	X					X	
Chronic Fatigue Syndrome	4	5	0		X		X	X		
Chronic Liver Disease and Cirrhosis	241	274	37	X		X		X		
Chronic Obstructive Pulmonary Disease	75	96	18					X		
Climate Change	4	4	2	X		X				
Clinical Research	9,629	10,336	1,854	X	X	X	X	X	X	X

Estimates of Funding for Various Research, Condition, and Disease Categories

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Clinical Trials	3,562	2,966	485	X	X	X	X	X	X	X
Colo-Rectal Cancer	274	281	48	X						X
Comparative Effectiveness Research	+	194	246	X	X	X	X	X	X	X
Complementary and Alternative Medicine	430	513	70	X	X	X		X		X
Conditions Affecting Unborn Children	81	95	8		X	X			X	
Contraception/ Reproduction	473	427	65						X	
Cooley's Anemia	22	21	3					X		
Cost-Effectiveness Research	49	52	16	X	X	X		X		X
Crohn's Disease	51	55	14				X	X		
Cystic Fibrosis	90	86	13			X	X	X		
Dental/Oral and Craniofacial Disease	463	490	75	X	X	X	X	X	X	X
Depression	402	402	48		X			X	X	

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Diabetes[204]	1,080	1,030	121		X		X	X	X	X
Diagnostic Radiology	1,095	976	206	X	X			X		
Diethylstilbestrol (DES)	4	4	1	X						
Digestive Diseases	1,426	1,538	243	X	X	X	X	X		
Digestive Diseases (Gallbladder)	7	7	1					X		
Digestive Diseases (Peptic Ulcer)	14	17	3			X	X	X		X
Down Syndrome	17	18	4		X				X	
Drug Abuse (NIDA only) [205]	1,007	1,040	135	X	X	X		X	X	X
Duchenne/Becker Muscular Dystrophy	22	27	6		X			X		
Dystonia	15	16	2		X					
Eating Disorders	+	26	5		X				X	X
Emerging Infectious Diseases	2,098	2,080	307	X		X				
Emphysema	29	28	11	X						

Estimates of Funding for Various Research, Condition, and Disease Categories

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Endometriosis	15	15	2	X				X	X	
Epilepsy	145	128	21		X					
Estrogen	245	235	34	X	X				X	
Eye Disease and Disorders of Vision	796	862	129		X			X		
Facioscapulohumeral Muscular Dystrophy	3	3	2		X					
Fetal Alcohol Syndrome	34	34	7		X				X	X
Fibroid Tumors (Uterine)	16	18	2	X				X	X	
Fibromyalgia	12	11	2		X					
Food Safety	244	262	37			X				
Fragile X Syndrome	26	27	5	X	X				X	
Frontotemporal Dementia (FTD)	17	22	2		X				X	
Gene Therapy	249	221	28	X	X	X	X	X		
Gene Therapy Clinical Trials	16	11	0	X	X	X	X	X		

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Genetic Testing	383	316	76	X					X	
Genetics	6,872	7,278	1,676	X	X	X	X	X	X	X
Global Warming Climate Change	1	3	1			X				
Health Disparities [206]	2,614	2,806	434	X	X	X	X	X	X	X
Health Effects of Climate Change	286	179	35	X		X				
Health Services	743	1,102	316	X	X	X	X	X	X	X
Heart Disease	1,217	1,202	227					X	X	X
Heart Disease - Coronary Heart Disease	367	426	98					X	X	X
Hematology	894	908	151	X		X	X	X		
Hepatitis	180	178	23	X		X		X		
Hepatitis - A	6	4	0			X				
Hepatitis - B	53	51	6	X		X		X		X
Hepatitis - C	93	97	12	X		X		X		

Estimates of Funding for Various Research, Condition, and Disease Categories

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
HIV/AIDS [207,208]	2,928	3,019	319	X	X	X			X	X
Hodgkin's Disease	16	26	1	X						
HPV and/or Cervical Cancer Vaccines	19	25	2	X		X			X	
Human Fetal Tissue [209]	40	41	22	X	X	X	X			
Human Genome	1,259	1,775	566	X	X			X		
Huntington's Disease	51	57	12		X					
Hyperbaric Oxygen	4	3	0		X					
Hypertension	263	266	41		X			X	X	X
Immunization	1,734	1,773	191	X	X	X			X	X
Infant Mortality/(LBW)	246	246	32		X	X			X	X
Infectious Diseases	3,575	3,627	526	X	X	X				X
Infertility	73	75	17						X	
Inflammatory Bowel Disease	81	91	22	X			X			

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Influenza	204	316	46			X				
Injury (total) Accidents/Adverse Effects	299	340	58		X				X	X
Injury - Childhood Injuries	26	33	3						X	
Injury - Trauma - (Head and Spine)	150	161	33		X				X	
Injury - Traumatic Brain Injury	59	71	15		X				X	
Injury - Unintentional Childhood Injury	15	19	1		X				X	
Interstitial Cystitis	10	11	1					X		
Kidney Disease	523	570	85	X	X	X		X		X
Lead Poisoning	9	11	3		X				X	
Liver Cancer	89	94	12	X						X
Liver Disease	562	572	79			X		X		
Lung	1,211	1,265	234	X				X		
Lung Cancer	169	178	36	X						

Estimates of Funding for Various Research, Condition, and Disease Categories

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Lupus	126	115	19		X		X			
Lyme Disease	22	25	5		X	X				
Lymphoma	193	184	22	X	X	X	X			
Macular Degeneration	135	85	8		X			X	X	
Malaria	132	110	11			X				
Malaria Vaccine	32	34	3			X				
Mental Health	2,086	2,129	382		X			X	X	X
Mental Retardation (Intellectual and Developmental Disabilities (IDD))	350	281	94		X				X	
Methamphetamine	67	69	13		X					X
Mind and Body	567	494	90	X	X			X		
Minority Health [210]	2,396	2,592	378	X	X	X	X	X	X	X
Mucopolysaccharidoses (MPS)	7	7	0	X	X			X	X	
Multiple Sclerosis	169	137	25		X		X			

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
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Muscular Dystrophy	56	66	17		X			X		
Myasthenia Gravis	9	9	3		X		X			
Myotonic Dystrophy	9	9	4		X					
Nanotechnology [211]	304	343	73	X	X	X				
Networking Information Technology R&D [212]	911	1,174	168	X						
Neurodegenerative	1,621	1,553	262		X					
Neurofibromatosis	14	17	2	X	X					
Neuropathy	121	119	13	X	X			X		
Neurosciences	5,224	5,320	848	X	X	X	X	X	X	X
Nutrition	1,391	1,400	205	X	X	X		X	X	X
Obesity	664	745	117	X	X			X	X	X
Organ Transplantation	175	139	32	X			X	X		
Orphan Drug	645	441	118	X	X	X	X			
Osteogenesis Imperfecta	5	5	1					X		

Estimates of Funding for Various Research, Condition, and Disease Categories

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Osteoporosis	183	198	21					X	X	
Otitis Media	18	15	7			X		X		
Ovarian Cancer	96	102	13	X						
Paget's Disease	1	1	1					X		
Pain Conditions - Chronic	279	333	53	X	X			X		
Parkinson's Disease	152	162	24		X					
Pediatric	2,771	2,996	505	X	X	X	X	X	X	X
Pediatric AIDS [213]	241	227	20	X	X	X			X	
Pediatric Research Initiative	209	214	256		X	X			X	
Pelvic Inflammatory Disease	3	3	1	X		X			X	
Perinatal - Birth - Preterm (LBW)	197	177	23		X	X			X	
Perinatal - Neonatal Respiratory Distress Syndrome	18	31	5						X	
Perinatal Period - Conditions	449	470	65		X				X	

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	**FY 2008**	**FY 2009 Non-ARRA**	**FY 2009 ARRA**	**Cancer**	**Neuroscience and Disorders of the Nervous System**	**Infectious Diseases and Biodefense**	**Autoimmune Diseases**	**Chronic Diseases and Organ Systems[202]**	**Life Stages, Human Development, and Rehabilitation**	**Minority Health and Health Disparities**
Originating in Perinatal Period										
Pick's Disease	2	2	-		X				X	
Pneumonia	93	108	15			X				
Pneumonia & Influenza	295	392	58			X				
Polycystic Kidney Disease	41	38	7	X				X		
Prevention	4,623	5,332	844	X	X	X	X	X	X	X
Prostate Cancer	290	310	47	X						X
Psoriasis	8	13	3				X			
Regenerative Medicine	723	799	144	X	X	X	X	X	X	
Rehabilitation	403	404	75	X	X				X	
Rett Syndrome	9	9	4		X				X	
Reye's Syndrome	0	-	-						X	
Rural Health	170	186	42	X	X	X				X

Estimates of Funding for Various Research, Condition, and Disease Categories

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Schizophrenia	249	265	85		X			X	X	
Scleroderma	20	21	2				X			
Septicemia	95	92	19			X				
Sexually Transmitted Diseases/Herpes	245	250	43	X	X	X			X	X
Sickle Cell Disease	80	63	14		X			X		
Sleep Research	225	217	33		X			X		
Small Pox	94	94	4			X				
Smoking and Health	310	329	78	X	X			X	X	X
Spina Bifida	15	14	3		X				X	
Spinal Cord Injury	80	80	14		X				X	
Spinal Muscular Atrophy	10	11	3		X					
Stem Cell Research	938	1,044	187	X	X	X	X	X	X	
Stem Cell Research - Embryonic - Human [214]	88	120	23		X	X	X	X	X	

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
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Stem Cell Research - Embryonic - Non-Human	150	148	29	X	X	X	X	X	X	
Stem Cell Research - Nonembryonic - Human	297	339	58	X	X	X	X	X	X	
Stem Cell Research - Nonembryonic - Non-Human	497	550	88	X	X	X	X	X	X	
Stem Cell Research - Umbilical Cord Blood / Placenta	46	49	10	X	X	X	X	X	X	
Stem Cell Research- Umbilical Cord Blood/ Placenta - Human	38	42	9	X	X	X	X	X	X	
Stem Cell Research - Umbilical Cord Blood/ Placenta - Non-Human	9	10	1	X	X	X	X	X	X	
Stroke	296	329	54		X				X	X
Substance Abuse [215]	1,763	1,653	245	X	X	X		X	X	X
Sudden Infant Death Syndrome	29	22	6		X				X	X

Estimates of Funding for Various Research, Condition, and Disease Categories

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	FY 2008	FY 2009 Non-ARRA	FY 2009 ARRA	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[202]	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities
Suicide	39	36	15		X				X	
Teenage Pregnancy	21	23	5						X	
Temporomandibular Muscle/Joint Disorder	19	15	1		X			X		
Tobacco	311	331	78	X	X			X	X	
Topical Microbicides	102	92	7			X			X	
Tourette Syndrome	8	7	3		X					
Transmissible Spongiform Encephalopathy (TSE)	44	43	4		X	X				
Transplantation	519	571	94	X	X		X	X		
Tuberculosis	142	189	27			X				
Tuberculosis Vaccine	18	15	3			X				
Tuberous Sclerosis	20	20	3		X					
Urologic Diseases	534	578	81	X		X		X		
Uterine Cancer	16	25	4	X						
Vaccine Related	1,632	1,593	185	X	X	X			X	

	Dollars in Millions (Actual)			Biennial Report Disease, Disorder, and Adverse Health Condition Topics						
Research/Disease Area	**FY 2008**	**FY 2009 Non-ARRA**	**FY 2009 ARRA**	**Cancer**	**Neuroscience and Disorders of the Nervous System**	**Infectious Diseases and Biodefense**	**Autoimmune Diseases**	**Chronic Diseases and Organ Systems[202]**	**Life Stages, Human Development, and Rehabilitation**	**Minority Health and Health Disparities**
Vaccine Related (AIDS)[216]	556	561	35	X		X				
Vector-Borne Diseases	417	401	66			X				
Violence Research	183	182	21							X
Vulvodynia	+	1	1		X				X	
West Nile Virus	39	59	7			X				
Women's Health [217]	3,514	3,725	506	X	X	X	X	X	X	X

[202] Chronic diseases and organ systems pertain to almost every area listed in the table. Instead of checking most areas, only the areas addressed in this chapter's section on chronic disease are checked.
[203] Reporting for this category does not follow the standard RCDC process. The total amount reported is consistent with reporting requirements for this category to the U.S. Office of Management & Budget (OMB). The project listing does not include non-project or other support costs associated with the annual total for this category. Additional information on this category is available at http://www3.niaid.nih.gov/topics/BiodefenseRelated/default.htm
[204] Includes research funded from the Type 1 diabetes appropriation of $150,000,000. These are project listings only.
[205] Reporting for this category does not follow the standard RCDC process. Spending is reported consistent with U.S. Office of National Drug Control Policy (ONDCP) requirements (Only NIDA). More information on this area is available at http://www.nida.nih.gov/drugpages.html.
[206] Reporting for this category does not follow the standard RCDC process. This category assigns project funding according to populations tracked by gender or ethnicity. The databases used to track gender/ethnicity are complex and not currently compatible with the RCDC system.
[207] Reporting for this category does not follow the standard RCDC process. These are project listings only and non-project or other support costs associated with the annual total for the category are not included. More information on this area is available at http://www.oar.nih.gov/.
[208] Includes research on HIV/AIDS, its associated opportunistic infections, malignancies, and clinical manifestations as well as basic science that also benefits a wide spectrum of non-AIDS disease research.
[209] Reporting for this category does not follow the standard RCDC process. This category uses a non-standard approach involving subject matter expert reviews of manually collected project listings.
[210] Reporting for this category does not follow the standard RCDC process. This category assigns project funding according to populations tracked by gender or ethnicity. The databases used to track gender/ethnicity are complex and not currently compatible with the RCDC system.
[211] The data provided reflects funding amounts reported by the NIH RCDC process for this category. Actual and estimate levels presented on this site supersede FY 2009-2011 amounts detailed in OMB MAX DE application tables that were based on preliminary FY 2009 funding support information.
[212] Ibid.
[213] Reporting for this category does not follow the standard RCDC process. These are project listings only and non-project or other support costs associated with the annual total for the category are not included. More information on the budget associated with the category is available at http://www.oar.nih.gov/. Research reported for this category is also captured under the broader HIV/AIDS category.
[214] Human embryonic stem cell research projects awarded with restrictions may have been included in the FY 2009 report.
[215] Reporting for this category does not follow the standard RCDC process. This category includes all spending reported under the Drug Abuse category as well as projects categorized under the broader area of Substance Abuse. These are project listings only. More information on this area is available at http://www.nida.nih.gov/drugpages.html.
[216] Reporting for this category does not follow the standard RCDC process. These are project listings only and non-project or other support costs associated with the annual total for the category are not included. More information on the budget associated with the category is available at http://www.oar.nih.gov/. Research reported for this category is also captured under the broader HIV/AIDS category.
[217] Reporting for this category does not follow the standard RCDC process. This category assigns project funding according to populations tracked by gender or ethnicity. The databases used to track gender/ethnicity are complex and not currently compatible with the RCDC system.

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3 SUMMARY OF RESEARCH ACTIVITES BY KEY APPROACH AND RESOURCE

Biennial Report of the Director

National Institutes of Health

Fiscal Years 2008 & 2009

Volume III

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National Institutes of Health

An electronic version of this report is available at: http://biennialreport.nih.gov and contains many live links to NIH programs, plans, and publications.

Volume III Contents

Contents of Other Volumes

Epidemiological and Longitudinal Studies

In 2008, the world's most comprehensive and longest running longitudinal examination of human aging celebrated an astonishing 50 years of groundbreaking research that has transformed the field of geriatrics. Since its establishment in 1958, the NIH-supported Baltimore Longitudinal Study of Aging (BLSA) has provided a wealth of information on the physical consequences of aging and has helped distinguish changes due to aging from those due to disease. For example, BLSA scientists have elucidated the relationship between age-related changes in the arteries and cardiovascular disease and also have distinguished normal age-related declines in cognitive ability from those associated with Alzheimer's disease and related conditions. In 2009, BLSA launched a new initiative called IDEAL (Insight into the Determinants of Exceptional Aging and Longevity), which will study people 80 years of age and older who are living free of physical and cognitive disease. This effort will help identify the genetic, environmental, social, and behavioral factors that allow some individuals to enjoy excellent health well into their 80s while others experience disease and physical decline earlier in life.

Introduction

Epidemiological studies examine factors that contribute to health and disease in human populations using a broad range of approaches. Persons or groups can be followed over time in longitudinal studies, or a snapshot of information can be collected at a single point in time. Studies can be done retrospectively, examining outcomes that have already occurred and factors that may have contributed to health or disease, or they can be done prospectively by beginning to monitor a population of interest before a particular disease-related outcome occurs. Many epidemiological studies are observational in nature, collecting information about and comparing groups—called cohorts—made up of individuals who share a characteristic of interest (e.g., tobacco use, age, educational status). Population studies are another type of epidemiological research, aimed at providing a better understanding of populations—how they change in size, composition, and distribution; the complex social, economic, and cultural factors that cause such changes; and the consequences of population change for health and well-being at the individual and societal levels.

Epidemiological research is a critical part of the activities undertaken to fulfill the NIH mission of pursuing fundamental knowledge of living systems and applying that knowledge to extend healthy life and reduce the burdens of illness and disability. Epidemiological research is important for investigating all types of disease and draws on expertise from a wide range of disciplines; thus, it is not surprising that virtually all NIH ICs are involved with epidemiological research in some capacity. As part of the continuum from basic to applied research, epidemiological and longitudinal studies often test the findings of laboratory or clinical research at the population level. For example, animal studies demonstrating the reproductive and neurological effects of bisphenol A (BPA)—a common component of plastics—have prompted large-scale epidemiological studies to ascertain the exposure and health effects of this chemical in humans. Additionally, observations made through epidemiological studies often result in the formulation of new or modified hypotheses that spur new basic, translational, and clinical studies. For example, epidemiological studies in the 1950s showing that tobacco smoking increases risk of lung cancer led to extensive research to identify the carcinogens and mechanisms involved in tobacco-related carcinogenesis. Thus, epidemiological and longitudinal studies are essential for linking bench to bedside to population.

Animal studies demonstrating the reproductive and neurological effects of bisphenol A (BPA)—a common component of plastics—have prompted large-scale epidemiological studies to ascertain the exposure and health effects of this chemical in humans.

The population-based perspective provided by epidemiological studies often helps to form a foundation for the practical application of scientific knowledge, such as changes in clinical practice and the development of public policy. For example, the Framingham Heart Study, which was initiated in 1948, linked risk of cardiovascular disease, which was rapidly becoming a major public health concern by the middle of the 20th century, to factors such as high serum cholesterol levels, hypertension, and cigarette smoking. Based on these results, clinicians were better able to identify

patients at high risk for cardiovascular disease. More recently, a series of NIH studies revealed an increased risk of cancer following exposure to benzene at levels below 10 parts per million and documented blood toxicity following exposure levels of under 1 part per million.[1, 2] These data were used by the U.S. Environmental Protection Agency (EPA) as it developed a new rule in 2007 that limits the benzene content in gasoline and adopts new standards for passenger vehicles and portable fuel containers to limit emissions of benzene and other hazardous air pollutants.[3]

Many of the NIH-supported epidemiological studies described in this section will inform future clinical practice guidelines and public policy, although it sometimes takes decades for the fruits of these large-scale, long-term studies to be realized. As the Nation's leading Federal agency for biomedical research, NIH is well suited to conduct these sorts of studies. Its stable infrastructure allows it to invest in the types of decades-long projects that are particularly informative for studying factors that contribute to disease development. Furthermore, NIH fosters team science among and between intramural and extramural scientists with diverse expertise, facilitating multidisciplinary studies that lead to a comprehensive understanding of health and disease.

Catalog of Epidemiological & Longitudinal Research Activities

Currently, NIH does not collect the information necessary for a catalog of epidemiological studies and longitudinal studies. This capacity is expected to be developed in the future for integration with RCDC.

Summary of NIH Activities

Although not comprehensive, the following summary highlights several ongoing NIH-supported epidemiological and longitudinal studies. These examples illustrate the strengths of NIH's epidemiological research portfolio: continuing efforts to make the most of past investments, an appreciation of the myriad factors that contribute to health and disease, and cooperation within and beyond the biomedical research community to achieve outcomes relevant to public health.

Investments in the Past Continue to Pay Off

NIH has been investing in epidemiological and longitudinal studies for most of its history. Some of these studies have been ongoing for decades. For example, the Framingham Heart Study has been running for more than 60 years. The infrastructure created and data collected from these studies continue to advance understanding of disease and health in new and exciting ways. Prolonged follow up also has enormously increased the value of these studies, and their existence helps form the foundation for extraordinary opportunities in biomedical research today.

NIH has been investing in epidemiological and longitudinal studies for most of its history. Some of these studies have been ongoing for decades.

Continuing to Follow Existing Cohorts

It has become clear that many of the factors contributing to health and disease are present and begin to exert their influence long before clinical presentation of a problem. NIH-supported longitudinal studies of many cohorts conducted over the past several decades are continuing to elucidate how diverse factors integrate and interact to contribute to disease over time as well as answering new research questions. The National Longitudinal Study of Adolescent Health (Add Health) is one example. It was established as a joint effort of 18 NIH Institutes and other Federal offices to examine how families, peers, schools, and neighborhoods influence the health-related behaviors of teens and their use of health care. During the first wave of the study in 1994-1995, information was collected through administration of more than 90,000 surveys to students in grades 7 through 12 and 20,000 at-home interviews with students and their parents. Follow up was conducted with the adolescents 1 year later and again in 2001-2002. Another round of follow up with the original Add Health cohort, now 24 to 32 years of age, was initiated in 2008. The social, behavioral, environmental, and biological data collected through this wave of the study will provide insight into developmental and health trajectories as adolescents

move into young adulthood and assume adult roles and responsibilities. For example, one recent analysis revealed that individuals who married or moved in with a partner were more likely to become obese than those who were dating, suggesting that interventions targeted at those establishing a shared household may be useful.[4] More than 600 publications have been generated based on Add Health data, which continue to be available for both scientific study and policy analyses.

The social, behavioral, environmental, and biological data collected through the National Longitudinal Study of Adolescent Health (Add Health) study will provide insight into developmental and health trajectories as adolescents move into young adulthood and assume adult roles and responsibilities.

Using Specimens from Existing Cohorts to Identify Genetic Markers of Disease

In addition to following cohorts for extended periods of time, NIH is leveraging its past and current investments in population-based studies to study the genetic basis of disease. The Cancer Genetic Markers of Susceptibility (CGEMS) project has conducted genome-wide association studies (GWAS) to identify genetic variants associated with risk of prostate and breast cancer using specimens from 11 existing cohorts. CGEMS researchers have identified new genetic variants in two regions of DNA (located on chromosomes 1 and 14) that may be associated with risk of sporadic breast cancer, as well as regions of chromosomes 7, 8, 10, and 11 that are associated with moderate increases in the risk of prostate cancer.[5, 6, 7] The same region on chromosome 8 also may be involved in colon cancer and certain other tumors, suggesting a novel pathway of cancer susceptibility shared by a variety of cancers.

The Cancer Genetic Markers of Susceptibility project has identified genetic variants associated with breast and prostate cancer, as well as a chromosomal region of shared susceptibility for several other cancers.

Another NIH initiative called the SHARe (SNP Health Association Resource) project also is conducting GWAS on several large cohorts to elucidate genetic contributors to disease. One of the cohorts being examined as part of SHARe is that of the Framingham Heart Study. The Framingham cohort was first established in 1948 and has since been expanded to include the children and grandchildren of the original participants. As part of SHARe, the DNA of more than 9,000 Framingham participants from all three generations has been analyzed. These genetic data, along with information about major disease risk factors (e.g., systolic blood pressure, cholesterol levels, cigarette use), have been added to dbGaP (the database of Genotypes and Phenotypes) and are available for use by researchers interested in investigating genetic contributors to disease.

Gaining Insights for Policy from Long-Term Population-Based Studies

Long-term NIH studies also have been used to inform the decisions of policymakers and assess the short- and long-term effects of policies on health or health-related behaviors. In 1975, NIH launched Monitoring the Future (MTF), a study that tracks the beliefs, attitudes, and behaviors of adolescents and young adults. MTF surveys approximately 50,000 students in grades 8, 10, and 12 each year. In addition, follow up is conducted with a subset of each graduating class until they reach age 30. Among other things, MTF gathers information on alcohol and other drug use, allowing identification of emerging substance abuse trends as well as factors contributing to them. MTF data have informed policy discussions on substance abuse and have been used by the White House Office of National Drug Control Policy to monitor progress toward national health goals. The most recent MTF survey, conducted in 2008, found that the rate of cigarette smoking was the lowest it has been in the 33-year history of the survey. The survey also revealed a 25 percent decline since 2001 in student reports of illicit drug use in the past month. However, after exhibiting consistent declines since the mid-1990s, marijuana use appears to have leveled off. Moreover, prescription drugs are now among those most commonly abused by high school seniors, following marijuana, alcohol, and tobacco.[8]

In 2008, the Monitoring the Future study found that the rate of cigarette smoking among students in grades 8, 10, and 12 was the lowest it has been in the 33-year history of the survey.

The increasing age of the U.S. population has major implications for policy. The NIH Health and Retirement Study (HRS) collects multidisciplinary data about the physical and mental health, insurance coverage, financial situations, family support systems, work status, and retirement planning of Americans over age 50 to help inform policy decisions. Now in its 16th year, HRS surveys more than 22,000 Americans every 2 years. Nearly 1,000 researchers have used HRS data to publish more than 1,000 reports, including more than 600 peer-reviewed journal articles and book chapters, and 70 doctoral dissertations.[9] Recently, HRS data were used to measure health insurance coverage trends as people approach and pass the age of eligibility for Medicare. The analysis found differential results for particular populations. For example, people who were unmarried or individuals in particularly good or poor health had an increased likelihood of being uninsured prior to becoming eligible for Medicare. Individuals in good health may have believed they did not need insurance while those in poor health may not have been able to obtain coverage. Nonwhites and those in good health had an increased likelihood of having Medicare-only coverage after reaching the age of eligibility for Medicare.[10]

Pursuit of a Comprehensive Understanding of Health and Disease

A comprehensive understanding of health and disease requires consideration of factors from the molecular to the community level. Integration of this information necessitates a systems approach that takes into account genetics, biology, and the social sciences. Conducting studies in diverse contexts helps to elucidate how these contributors converge to influence health and also ensures that insights gained will benefit different populations. NIH supports a number of studies in the United States and worldwide aimed at building a comprehensive understanding of disease and health with the goal of identifying new and more effective approaches for prevention and treatment.

Determining How Genes and Environment Interact to Influence Disease Risk

With the availability of high-throughput sequencing technology and the completion of the Human Genome Project, research on the genetic basis of disease has exploded over the past 2 decades. More recently, it has become clear that environmental factors can have a strong influence on how genetic background affects disease risk. To facilitate research on the interactions of genes and the environment, NIH has launched a large volunteer DNA-banking project called the Environmental Polymorphism Registry (EPR). The goal of the EPR is to collect DNA samples from 20,000 individuals to allow scientists to study how genes contribute to diseases such as diabetes, heart disease, cancer, asthma, and many others. The study participants are in the greater Research Triangle Park region of North Carolina, which has a diverse population in terms of age, ethnicity, economic and educational background, and health status. Unlike anonymous DNA registries, researchers using EPR are able to identify and contact registry participants—with their consent—for further study if they are found to have potentially significant genetic variants. Another unique feature of the EPR is that two distinct populations are solicited for participation: an apparently healthy population as well as a population recruited from various clinics and hospitals in the area. Individuals in the clinic population have an array of medical conditions; their inclusion in the EPR increases the likelihood of identifying subjects with both the genetic and clinical characteristics of interest. These aspects of the EPR give scientists the flexibility to design follow-up studies while reducing biases that can occur in genetic epidemiology studies when subjects are recruited based primarily on their observable clinical or physical traits. Although many genes will be studied as part of the EPR, the focus will be on so-called "environmental response genes" that increase or decrease disease risk when combined with an environmental exposure.

The Environmental Polymorphism Registry will collect DNA from 20,000 people to allow scientists to study how genes contribute to diseases such as diabetes, heart disease, cancer, asthma, and many others.

Through the Breast Cancer and the Environment Research Centers (BCERC), NIH is studying how interactions of chemical, physical, and social factors, combined with genetic factors, affect breast development during puberty and breast

cancer predisposition. An epidemiologic study being conducted as part of BCERC is prospectively following through puberty a cohort of multiethnic 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet influences fat tissue and alters the effects of hormones on sexual maturation. Endocrine disruptors, irradiation, and psychosocial elements also will be studied for effects. The BCERC directly relates to one of NIH's Government Performance and Results Act (GPRA) goals: By 2011, conduct studies of girls aged 6 through 8 years to determine the associations of 12 environmental exposures with age of onset of puberty and progression through puberty (SRO-5.10).

Improving Treatment and Prevention

In addition to providing a more complete picture of disease, multidisciplinary involvement is crucial for generating results with practical implications for clinical practice or behavior. Several ongoing NIH studies have the potential to alter clinical practice to improve health and minimize the burden of disease. The Oral HIV/AIDS Research Alliance (OHARA) is part of the AIDS Clinical Trials Group, the world's largest HIV clinical trials organization. OHARA drives and supports studies in the United States and internationally to improve diagnosis, treatment, and management of AIDS-related oral complications. These complications—which include ulcers and tumors, fungal infections, and painful viral lesions—occur in nearly all of the 33 million HIV-infected people worldwide and can compromise nutrition and exacerbate immune suppression. Although antiretroviral therapy alleviates some of the symptoms, many oral lesions require additional specific treatment. NIH provides central management and leadership for OHARA researchers, which include experts in epidemiology, mycology, and virology.

Through the COPDGene study, NIH is performing genetic testing in more than 10,000 current or former smokers to identify genetic characteristics associated with the presence of chronic obstructive pulmonary disease (COPD). This research should help reveal why some smokers develop serious lung disease while others do not. In addition to helping clinicians identify smokers at high risk for COPD, the study results likely will reveal molecular pathways involved in the pathogenesis of the disease that may be targets for prevention or therapy.

Identifying Disease Risk among Diverse Populations

Research has shown that factors such as genetic background, geographic location, socioeconomic status, and cultural traits can result in variations in disease risk among different populations. This observation has important implications for biomedical research, as results in one population may not necessarily apply to another. Thus, it is important to include study participants with diverse backgrounds and characteristics to increase the likelihood that insights gained through study findings will benefit all groups of people. In this regard, NIH is supporting the Multi-Ethnic Study of Atherosclerosis (MESA), a multicenter epidemiological study of cardiovascular disease in men and women from four ethnic groups—white, African American, Hispanic, and Chinese. This study, which began in 1999, has measured and compared the value of chest computed tomography (CT), cardiac magnetic resonance imaging, carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for predicting the development of cardiovascular disease. In one recent study, researchers used MESA data to confirm that CT measurements of coronary calcium, previously shown to predict coronary heart disease among white populations, are effective predictors in African Americans, Hispanics, and Chinese as well.[11] Clinical and genomic data from the MESA cohort will be made available to the research community through SHARe to facilitate GWAS.

The Multi-Ethnic Study of Atherosclerosis is studying cardiovascular disease in white, African American, Hispanic, and Chinese populations.

Culture of Cooperation to Promote Public Health

Bridging the gap between research and application requires the contributions of numerous scientists with diverse expertise. NIH therefore fosters a culture of cooperation, encouraging researchers to build teams capable of designing and conducting research with identified potential to improve public health.

Teaming Up to Improve the Study of Disease

Recognizing the need for large-scale collaborations to study the role of gene-gene and gene-environment interactions in the etiology of cancer, NIH formed the Cohort Consortium. The mission of the Consortium—which currently comprises 37 cohorts and more than 4 million individuals—is to foster communication among investigators leading cohort studies of cancer; promote collaborative projects for topics not easily addressed in a single study; and identify common challenges in cohort research and search for solutions. Investigators team up to use common protocols and methods to facilitate parallel and pooled analyses of data. In addition to the CGEMS initiative (described above), another project of the Cohort Consortium is the Pancreatic Cancer Cohort Consortium in which investigators from 12 prospective epidemiologic cohort studies and 1 case-control study are collaborating to carry out whole-genome scans of common genetic variants to identify markers of susceptibility to pancreatic cancer.

Bringing Together NIH Institutes and Centers

The 27 NIH ICs collectively house expertise on a broad spectrum of diseases, populations, and research support methods. Large-scale epidemiological studies provide an ideal opportunity for researchers from the various NIH components to come together to conduct innovative studies on the diverse factors that coalesce to influence public health and disease. One example of collaboration among NIH ICs is the Hispanic Community Health Study, which is sponsored by six NIH Institutes (NHLBI, NCMHD, NIDCD, NIDCR, NIDDK, and NINDS) and the NIH Office of Dietary Supplements. This multicenter study aims to recruit 16,000 persons of Hispanic/Latino descent, with a focus on individuals with Cuban, Puerto Rican, Mexican, and Central/South American ancestry. Participants will undergo a series of physical examinations and interviews to identify factors that influence a wide variety of diseases, disorders, and conditions, including heart disease, asthma, sleep disorders, diabetes, cognitive impairment, and more. Particular attention will be given to the role of cultural adaptation and disparities in the prevalence and development of disease. The insights gained from this study will be invaluable because the U.S. Hispanic population, already the largest minority population in the country, is expected to triple by 2050.

The Hispanic Community Health Study will provide insight into the prevalence of and risk factors for a variety of diseases within the most rapidly growing ethnic population in the United States.

Collaborating with Other Federal Departments and Agencies

As the Nation's premiere biomedical research agency, NIH seizes the opportunity to collaborate with other Federal departments and agencies on projects related to health. One example of such an intergovernmental collaboration is the Agricultural Health Study (AHS), cosponsored by two NIH Institutes and EPA. With a cohort of more than 89,000 private and commercial pesticide applicators and their spouses, the study is exploring occupational, lifestyle, and genetic factors that may affect the rate of diseases in farming populations. Although current medical research suggests that agricultural workers are healthier overall than the general U.S. population, they may have higher rates of some types of cancer and other conditions like asthma, neurologic disease, and reproductive problems. A recent AHS study found that elevated exposure to certain pesticides was associated with a doubling of the risk of adult-onset asthma.[12] Another study evaluated the relationship between lifetime exposure to pesticides and diabetes; of the 50 pesticides evaluated, 7 were associated with an increased risk of diabetes. The strongest association was with the organophosphate insecticide trichlorfon.[13] Continuing identification of links between agricultural exposures and health problems will inform future policies designed to protect farmers, their families, and others who live or work in agricultural areas.

The Agricultural Health Study has linked exposure to certain pesticides to elevated risk of diabetes and adult-onset asthma.

NIH also is working with the U.S. Army to evaluate soldiers across all phases of Army service (e.g., predeployment training, deployment and noncombat assignments, and post-separation re-integration to civilian life) as part of the Collaborative Study of Suicidality and Mental Health in the U.S. Army. This study was prompted by growing concern over the high rates of mental health and behavioral adjustment problems, including substance abuse and addiction, among recent U.S. military combat veterans and increasing rates of suicide among soldiers. The goal of the study is to identify modifiable risk and protective factors for, as well as moderators of, suicide-related behaviors. In a separate effort, three NIH Institutes, in conjunction with the Department of Veterans Affairs, have issued a call for studies examining how trauma, stress, and substance use/abuse emerge in U.S. military personnel, veterans, and their families, with a focus on how these disorders can be prevented and treated. NIH also is launching a study of the impact of existing national, state, and/or local community-based programs that are addressing the re-entry/adjustment and mental health needs of recent combat veterans. This initiative will inform strategic approaches to fostering the successful transition of all service members to civilian roles.

Conclusion

Epidemiological and longitudinal studies are essential to NIH's efforts to bridge the results of basic, translational, and clinical studies to practical applications such as clinical practice and public policy. Many NIH epidemiological and longitudinal studies have had substantial influence on public health, with current investments likely to follow suit. This success is due to a number of factors, including investment in long-term studies, pursuit of a comprehensive view of disease, and promotion of a culture of cooperation.

The studies described above represent only a fraction of NIH's efforts in this area. Epidemiological studies are being carried out by experts in a number of disciplines, including, but not limited to, epidemiology, behavioral and social sciences, genetics, molecular biology, public health, economics, statistics, and data management. Although still far from comprehensive, additional notable examples of NIH-supported epidemiological and longitudinal studies, as well as further information about some of the activities mentioned above, are found on the following pages.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Investments in the Past Continue to Pay Off

Population Research: Given the Nation's increasing diversity and changing demographics, it is critical to understand how trends in such areas as immigration, fertility, marriage patterns, and family formation affect the well-being of children and families. NIH research in these areas allows policymakers and program planners to better address public health needs. For instance:

- The Fragile Families and Child Well-Being Study follows children born to unmarried parents to assess how economic resources, father involvement, and parenting practices affect children's development.
- The New Immigrant Survey follows the first nationally representative sample of legal immigrants to the United States, providing accurate data on legal immigrants' employment, lifestyles, health, and schooling before and after entering the country.
- Several NIH Institutes are supporting The National Longitudinal Study of Adolescent Health, which integrates biomedical, behavioral, and social science data to discover the pathways that lead to health and/or disease in adulthood.

→ For more information, see http://www.cpc.unc.edu/addhealth/
→ For more information, see http://nis.princeton.edu/index.html
→ For more information, see http://www.fragilefamilies.princeton.edu/index.asp
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NICHD**, NCI, NCMHD, NIA, NIAAA, NIAID, NIDA, NIDCD, NINR, OAR, OBSSR, ORWH)

Genome-Wide Association Studies of Cancer Risk: The Cancer Genetic Markers of Susceptibility (CGEMS) project is a signature initiative that uses genome-wide association studies (GWAS) to identify genetic variants and mechanisms associated with cancer risk. Understanding these variants and mechanisms may lead to new preventive, diagnostic, and therapeutic interventions. CGEMS investigators have pinpointed genetic variants associated with elevated prostate cancer risk as well as variants associated with increased breast cancer risk. The same genetic variant was shown to be involved in increased prostate, colon, and other cancers, suggesting a common mechanistic pathway for susceptibility to a variety of cancers. Another GWAS project, the Cohort Consortium, is a unique extramural/intramural collaboration that allows Consortium partners to share access to data on 37 cohorts comprised of 4 million people from diverse populations. Each cohort contains extensive information on known or suspected risk factors and biospecimens collected pre- and post-diagnosis. The large number of study subjects permits the detection of modest genetic effects, as well as studies of variants involved in less common cancers. One cohort within the Consortium, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort, includes about 2.9 million specimens. These pre-diagnostic specimens provide a valuable resource for studies of cancer etiology and early detection. Researchers can correlate changes in molecular profiles associated with the onset of different types of disease, thereby providing valuable insights into the actual mechanisms of human carcinogenesis.

→ For more information, see http://cgems.cancer.gov
→ For more information, see http://epi.grants.cancer.gov/Consortia/cohort.html
→ For more information, see http://www.parplco.org
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Genomics*
→ (E/I) (**NCI**)

A Look at Drug Abuse Trends: Local to International: Two major systems of data collection are helping to identify substance abuse trends locally, nationally, and internationally: Monitoring the Future Survey (MTF) and the Community Epidemiology Work Group (CEWG). Both help to surface emerging drug abuse trends among adolescents and other populations, and guide responsive national and global prevention efforts. The MTF project, begun in 1975, has many purposes, the primary one being to track trends in substance use, attitudes, and beliefs among adolescents and young adults. The survey findings also have been used by the President's Office of National Drug Control Policy to monitor progress toward national health goals. The MTF project includes both cross-sectional and longitudinal formats—the former given annually to 8th, 10th, and 12th graders to see how answers change over time, and the latter given every 2 years (until age 30), then every 5 years to follow up on a randomly selected sample from each senior class. CEWG, established in 1976, provides both national and international information about drug abuse trends through a network of researchers from different geographic areas. Regular meetings feature presentations on selected topics, as well as those offering international perspectives on drug abuse patterns and trends. CEWG findings reported in 2008 and 2009

show decreases in methamphetamine indicators (e.g., treatment admissions), suggesting that the problems that had escalated in the first half of the decade may have stabilized or declined. Development of a Latin American Epidemiology Network is underway. NIH also has provided technical consultation for the planning and establishment of an Asian multicity epidemiological network on drug abuse.

→ For more information, see http://www.monitoringthefuture.org/
→ For more information, see http://www.drugabuse.gov/about/organization/CEWG/CEWGHome.html
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E) (**NIDA**)

Advances in Minority Mental Health Research: Results from NIH's Collaborative Psychiatric Epidemiology Surveys (CPES) have continued to shed light on the risk, prevalence, and outcomes associated with mental disorders in minority populations. Two CPES surveys, the National Latino and Asian American Study (NLAAS), and the National Survey of American Life (NSAL), are large, nationally representative epidemiologic surveys that focus, respectively, on the mental health epidemiology of Latinos and Asians, and African Americans. Examples of important research that has emerged from the CPES include an FY 2009 study from the NSAL that found that African American teens, especially girls, are at increased risk for suicide attempts, even if they have not been diagnosed with a mental disorder. The study's findings may be used to improve clinicians' screenings for suicidal behavior among adolescent African Americans. Additionally, an FY 2009 study using data from the NLAAS and the National Co-morbidity Survey Replication found that previous research showing native-born Latinos to be at higher risk for mental disorders than nonnative-born Latinos may not be true across all Latino subgroups. NLAAS researchers found that this widely reported phenomenon (the "immigrant paradox") was true in some subgroups, but it did not hold in others (e.g., among Puerto Ricans). The results emphasize the heterogeneity of the Latino population and suggest the importance of addressing this population's subgroups in future research.

→ Joe S, et al. *J Am Acad Child Adolesc Psychiatry* 2009;48(3):271-82. PMID: 19182692. PMCID: PMC2760075. Alegria M, et al. *Am J Psychiatry* 2008;165(3):359-69. PMID: 18245178. PMCID: PMC2712949.
→ For more information, see http://www.nimh.nih.gov/science-news/2009/black-teens-especially-girls-at-high-risk-for-suicide-attempts.shtml
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIMH**)

Demographic and Economic Studies of Aging: NIH supports a number of studies on the demographic and economic changes in our society. The Health and Retirement Study (HRS) is the leading source of combined data on health and financial circumstances of Americans over age 50 and a valuable resource to follow and predict trends and help inform policies for an aging America. Now in its 16th year, the HRS follows more than 20,000 people at 2-year intervals and provides researchers with an invaluable and growing body of multidisciplinary data on the physical and mental health of older Americans, insurance coverage, finances, family support systems, work status, and retirement planning. Recently, researchers used HRS data on memory and judgment of a large subset of HRS participants to determine trends in cognitive status of those age 70 and older. The researchers found that cognitive impairment dropped from 12.2 percent in 1993 to 8.7 percent in 2002. The study recently has been expanded to include additional key constructs in cognitive aging. NIH also has renewed its program of Centers on the Demography and Economics of Aging to foster research in the demography, economics, and epidemiology of aging and to promote the use of important datasets in the field. The achievements of this program in past years were recognized in September 2008 by the Heidelberg Award for Significant Contributions to the Field of Gerontology, a triennial international competition.

→ For more information, see http://hrsonline.isr.umich.edu
→ For more information, see http://agingcenters.org

→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIA**)

Database of Genotype and Phenotype (dbGaP): Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics, and other scientific data, NIH established dbGAP to house the results of genome-wide association studies (GWAS), which examine genetic data of de-identified subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2009, dbGaP included results from more than 40 GWAS, including genetic analyses related to such diseases as Parkinson's disease, ALS, diabetes, alcoholism, lung cancer, and Alzheimer's disease. dbGaP is the central repository for many NIH-funded GWAS to provide for rapid and widespread distribution of such data to researchers and accelerate the understanding of how genes affect the susceptibility to and severity of disease.

→ For more information, see http://view.ncbi.nlm.nih.gov/dbgap
→ This example also appears in Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**NLM**)

Epidemiologic Studies of Osteoporosis: NIH supports several prospective cohort studies, including the Study of Osteoporotic Fractures (SOF) in women and Mr. OS, a study of osteoporosis and other age-related diseases in men. The studies, which have been underway since 1986 and 1999, respectively, identified characteristics associated with fracture risk in older Americans. Assessing risk is important because the devastating consequences of low bone mass can be prevented. For example, simple changes to a person's home (e.g., adding more lights, removing clutter) can prevent falls. A balanced diet and modest exercise build bone strength, and medications can slow disease progression. SOF, Mr. OS, and other studies are providing information about osteoporosis diagnosis, treatment, and prevention. SOF and Mr. OS reinforced a notion, outlined in the Surgeon General's 2004 report on Bone Health and Osteoporosis, that older people who have a fracture should be tested for osteoporosis—even if the fracture occurred because of a traumatic injury (e.g., a fall off a ladder or an auto accident) that could hurt a healthy young person. Mr. OS is generating data that the U.S. Preventive Services Task Force can incorporate into guidance on using bone mineral density to assess fracture risk. Scientists using data from the Framingham Osteoporosis Study recently reported that men and women who consumed the most vitamin C had fewer hip fractures than those who consumed less vitamin C—a finding that may have implications for the recommended intakes established for vitamin C. Women's Health Initiative investigators demonstrated that low blood levels of vitamin D, which helps the body absorb calcium from food, also is associated with hip fracture risk.

→ Cawthon PM, et al. *J Bone Miner Res* 2009;24(10):1728-35. PMID: 19419308. PMCID: PMC2743283.
Cauley JA, et al. *Ann Intern Med* 2008;149(4):242-50. PMID: 18711154. PMCID: PMC2743412.
Mackey DC, et al. *JAMA* 2007;298(20):2381-8. PMID: 18042915.
Sahni S, et al. *Osteoporos Int* 2009;20(11):1853-61. PMID: 19347239. PMCID: PMC2766028.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/11_28.asp
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/low_vitD_hip_fracture.asp
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIAMS**, NCRR, NHLBI, NIA)

Pursuit of a Comprehensive Understanding of Health and Disease

Environmental Polymorphisms Registry: NIH, in collaboration with the University of North Carolina's General Clinical Research Center, has launched a large volunteer DNA banking project named the Environmental Polymorphisms Registry (EPR). The goal of the EPR is to collect DNA samples from 20,000 individuals in the greater Research Triangle Park region of North Carolina through local health care systems, study drives, health fairs, and other means. This area has a diverse population varying in age, ethnicity, economic and educational backgrounds, and health status. The EPR offers a valuable resource for human genomic studies, especially when compared to anonymous DNA registries. It was designed for scientists to screen for functionally significant alleles and to identify subpopulations of individuals with shared genotypes, and then correlate their genotypes with their phenotypes in a process known as "recruit-by-genotype." The value of the EPR lies in the ability to identify and then re-contact subjects with potentially significant polymorphisms for further study. A unique feature of the EPR is that two distinct populations are solicited, an apparently healthy population recruited from the general population as well as a clinic population recruited from various clinics and hospitals in the area. Individuals in the clinic population have a wide array of medical conditions, and their inclusion in the EPR increases the likelihood of identifying subjects with both the genotypes and phenotypes of interest. These aspects of the EPR give scientists more flexibility in designing follow-up studies while reducing the ascertainment bias that can occur in genetic epidemiology studies when subjects are recruited based on phenotype.

→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NIEHS**)

Understanding HIV, TB, and Malaria Co-infection: Tuberculosis (TB) is one of the leading causes of death among people living with HIV/AIDS and one of the most common opportunistic infections they experience. HIV and TB reinforce one another: HIV activates dormant TB in a person, who then becomes infectious and able to spread the TB bacillus to others. HIV infection increases the risk of getting TB by a factor of 20 or more, according to the World Health Organization. Similarly, many HIV-positive individuals are co-infected with malaria and face poorer treatment outcomes for both diseases. Notably, malaria infection in pregnant HIV-positive patients leads to worse outcomes for both the mother and the child. NIH is increasing its focus on TB co-infection with HIV, malaria, and other pathogens. Questions addressed include when to start antiretroviral therapy (ART) in patients co-infected with HIV and TB and how best to prevent development of active TB disease in HIV-infected individuals who are receiving ART. Other studies attempt to develop new diagnostics and TB treatments for individuals co-infected with TB and HIV. In addition, several studies underway assess how best to treat women and children with HIV and either TB or malaria. Finally, the Children with HIV and Malaria Project, a prospective, longitudinal study of Ugandan children, is designed to determine if HIV increases the risk of malaria in children, whether malaria is associated with accelerated HIV disease progression, if malaria treatment has a higher failure rate in HIV-infected children in comparison with HIV-uninfected children, and whether trimethoprim-sulfamethoxazole prophylaxis increases incidence of resistant malaria. The study enrolled 300 children with more than 3 years of follow-up, and concluded in September 2009.

→ For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/therapeutics/intro/drug_discovery.htm
→ For more information, see http://www3.niaid.nih.gov/topics/tuberculosis/
→ For more information, see http://www.who.int/entity/tb/challenges/hiv/tbhivbrochure.pdf
→ For more information, see http://www.unaids.org/en/policyandpractice/hivtreatment/coinfection/tb/default.asp
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIAID**)

The Sister Study: Environmental Risk Factors for Breast Cancer: The NIH Sister Study prospectively examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The frequency of relevant genes and shared risk factors is greater among sisters, increasing the ability of the study to detect risks. Researchers will collect data on potential risk factors and current health status, and will collect and bank blood, urine, and environmental samples for future use in studies of women who develop breast cancer or other diseases compared with those who do not. Analysis of new cases will assess the separate and combined effects of environmental exposures and genetic variations that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors like smoking, occupational exposures, alcohol, diet and obesity, and include analysis of phthalates, phytoestrogens, metals, insulin, growth factors, vitamins and nutrients, and genes in blood and urine. The study also allows investigators to examine a wide range of health outcomes of relevance to women, and to create a framework from which to test new hypotheses as they emerge. In addition to its focus on genetic and environmental causes of breast cancer, the prospective Sister Study tracks changes in health status over time. Among the chronic diseases currently studied are uterine fibroids and endometriosis, rheumatoid arthritis and other autoimmune diseases, thyroid disease, asthma, and cardiovascular diseases. As the cohort ages, the Sister Study will address aging-related health outcomes including osteoporosis, Parkinson's disease, and age-related cognitive decline.

→ For more information, see http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Minority Health and Health Disparities*
→ (E/I) (**NIEHS**, NCMHD)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects adipose tissue and alters hormonal control of sexual maturation. Endocrine distruptors, irradiation, and psychosocial elements also will be studied for effects.

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→ For more information, see http://www.bcerc.org/
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIEHS**, NCI) (GPRA)

Cancer Epidemiology Biomarkers and Prevention: The long-term Sister Study looks at the environmental and genetic characteristics of women whose sisters have had breast cancer to identify factors associated with developing breast cancer. A pilot study that was part of the Sister Study shows that women who maintain a healthy weight and who have lower perceived stress may be less likely to have chromosome changes associated with aging than obese and stressed women. Recently, NIH funded a study looking at 94 women whose breast cancer had spread or returned. Researchers asked the women whether they had ever experienced stressful or traumatic life events. The categories ranged from traumatic stress to some stress to no significant stress. The comparison revealed a significantly longer disease-free interval among women reporting no traumatic or stressful life events.

→ For more information, see http://www.niehs.nih.gov/news/releases/2009/sister-study.cfm
→ For more information, see http://www.nlm.nih.gov/medlineplus/magazine/issues/winter08/articles/winter08pg6b.html
→ This example also appears in Chapter 2: *Cancer*
→ (E/I) (**NCI**, NIA)

OHARA: The Oral HIV/AIDS Research Alliance: At the vanguard of basic, translational, and clinical research to combat the oral manifestations of HIV/AIDS is the NIH-funded Oral HIV/AIDS Research Alliance (OHARA), which drives and supports novel clinical studies in the United States and internationally to improve diagnosis, treatment, and management of comorbidities of AIDS-related oral complications, including necrotizing ulcers and tumors, fulminating fungal infections, and painful viral lesions that occur in almost all 33 million people infected worldwide. Their devastating effects compromise nutrition and exacerbate immune suppression in addition to the local effects. Even since the advent of antiretroviral therapy (ART), oral complications of AIDS remain a major public health problem. Though ART alleviates some symptoms, many oral lesions need additional specific treatment and globally, only 30 percent of HIV-infected individuals for whom ART is indicated receive it. The estimated prevalence of U.S cases of HIV/AIDS in 2006 exceeded 1.1 million, while about 56,300 people were newly infected with HIV that year. In its fourth year OHARA is making significant strides for people living with HIV/AIDS. OHARA is formed by world-expert scientists and clinicians. Its success is driven by three geographically and academically separate core units that provide expertise in epidemiology, mycology, and virology, embraced by a centralized NIH management and leadership. Currently, OHARA has ramped up eight clinical studies in various phases. They include studies to assess the clinical effectiveness of diagnostic tools for

HIV/AIDS-related conditions, and compare the safety and efficacy of novel treatments and preventive strategies for HIV/AIDS-related oral diseases and malignancies.

- → Shiboski CH, et al. *J Oral Pathol Med* 2009;38(6):481-8. PMID: 19594839.
  Jacobson MA, et al. *PLoS One* 2009;4(4):e5277. PMID: 19381272. PMCID: PMC2667217.
- → For more information, see http://aactg.org/committees/scientific/optimization-co-infection-and-co-morbidity-management/subcommittees/ohara-sub-3
- → For more information, see http://www.nidcr.nih.gov/Research/DER/IntegrativeBiologyAndInfectiousDiseases/AIDSImmuno.htm
- → For more information, see http://aactg.org/about-actg
- → For more information, see http://www.who.int/hiv/data/en/
- → For more information, see http://www.cdc.gov/hiv/topics/surveillance/basic.htm#Main
- → This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
- → (E) (**NIDCR**, NIAID)

The Role of Development in Drug Abuse Vulnerability: NIH supports animal, clinical, and epidemiological research across the lifespan to examine how developmental stage may influence drug abuse vulnerability or protection. The discovery of a protracted period of brain changes during early development and beyond has been critical to understanding the role of brain maturation in decision-making processes and responses to stimuli, including early (e.g., in utero) exposure to drugs. Adolescence has emerged as a particularly vulnerable period, during which an immature brain circuitry can translate into a preponderance of emotional reactivity (vs. higher cognitive control) that gives rise to the impulsive characteristics of many teenagers. This in turn may lead to dangerous risk-taking, such as experimenting with drugs that ultimately can lead to addiction. Using both animal models and clinical research, scientists are beginning to understand how environmental variables can play a key role in shaping brain maturation trajectories. In this regard, imaging, genetic, and epigenetic tools are helping interpret the effects of myriad environmental influences, such as quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics on brain development and behavior. In addition, the field of social neuroscience is harnessing the power of multidisciplinary approaches to tease apart these multilevel phenomena to better understand, for example, the neural mechanisms of peer pressure, the connections between chronic stress and risk of drug abuse initiation, and the impact that different early rearing environments can have on gene expression and behavior.

- → For more information, see http://www.nida.nih.gov/tib/prenatal.html
- → For more information, see http://www.nida.nih.gov/scienceofaddiction/
- → This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
- → (E) (**NIDA**, NICHD) (GPRA)

Following up on the Multimodal Treatment Study of Children with ADHD (MTA): Children with attention deficit hyperactivity disorder (ADHD), the most common of the psychiatric disorders that appear in childhood, often raise great concern from their parents and teachers because of their inability to focus on or finish tasks. Over time, these children may develop other emotional problems, including mood disorders, loss of self-esteem, and substance abuse. To address these issues, NIH is sponsoring an ongoing, multisite, follow-up of children from the MTA study—a treatment trial of nearly 600 ADHD-diagnosed elementary school children. Findings from the original MTA showed that long-term combination treatment (medication and psychosocial/behavioral treatment), as well as medication-management alone, significantly were superior to intensive behavioral treatments and routine community care in reducing ADHD symptoms. In the follow-up study (n = 485 10 to 13 year olds), children from this cohort and others who received similar pharmacotherapy were assessed for substance abuse outcomes. The study found that despite treatment, children with

ADHD showed significantly higher rates of delinquency and substance abuse. Follow-up of the MTA sample is continuing as the participating children go through adolescence and enter adulthood.

→ Molina BS, et al. *J Am Acad Child Adolesc Psychiatry* 2009;48(5):484-500. PMID: 19318991.
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0028.html
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0029.html
→ For more information, see http://www.nida.nih.gov/ResearchReports/comorbidity/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIDA**, NIMH)

The Early Childhood Longitudinal Study (ECLS) program: The National Center for Education Statistics, within the Institute of Education Sciences of the U.S. Department of Education, is conducting an ongoing study of a nationally representative sample of children from diverse socioeconomic and racial/ethnic backgrounds who will start kindergarten in 2011. Several Federal agencies, including NIH, are partnering on the study to determine how a variety of home, school, community, and student factors influence the transition of children to school; frame their early school experiences; shape their later school experiences; relate to normal cognitive, social, emotional, and physical child development; and affect academic performance over time. NIH is participating in a field test to work out logistics to determine the feasibility of adding a hearing and vision screening examination in the ECLS. ECLS is the only recent, nationally representative data collection program that enables statistical analysis of relationships between hearing and communication impairments or disorders and subsequent child development from infancy through eighth grade. The intent is to measure the hearing and vision of children during their first year of formal schooling, find out how hearing and vision change as a child grows, establish whether hearing and vision influence other aspects of normal child development, and clarify whether academic performance is influenced by hearing and vision. This information can be used then to evaluate how well early identification and intervention strategies were implemented during the birth cohort years from an earlier ECLS study.

→ For more information, see http://nces.ed.gov/ECLS/
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NEI, NIDCD**)

HIV/AIDS Epidemiological and Long-Term Cohort Studies: NIH continues its support of the largest HIV/AIDS observational studies in the United States, the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) of homosexual and bisexual men. These studies repeatedly have made major contributions to our understanding of HIV transmission, disease progression, and best treatment practices. The WIHS, now in its 16th year of research, studies the natural history of HIV infection and AIDS progression in 2,404 HIV-infected and uninfected women, and bridges the gap between theoretic benefits and sustainable gains of antiretroviral therapy. The MACS, now in its 26th year of research, studies the natural history of HIV infection and AIDS progression in 6,973 homosexual and bisexual men at sites located in Baltimore, Chicago, Pittsburgh, and Los Angeles. These domestic cohorts are on the forefront of research to define the clinical manifestations of long-term HIV/AIDS infection. Data from these cohorts have resulted in published studies on the long-term risk of HIV/AIDS on cardiovascular disease. Studies have been initiated on aging, sleep disorders, frailty, renal function, cognitive function, and behavior among HIV-infected persons.

→ For more information, see http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIAID**, NCI, NCRR, NICHD, NIDA)

Multicenter AIDS Study (MACS) Small Grant Opportunity: MACS is an ongoing (since 1984) epidemiological study in several U.S. cities of multi-ethnic/racial HIV-infected and HIV-uninfected men who have sex with men (MSM). A

small grant funding opportunity is enhancing the value and potential for new knowledge from the MACS by examining drug use and HIV/AIDS among MSM over the life course. Studies will include an examination of social and behavioral risk factors and trajectories, the role of drug use in neurocognitive function, and other medical consequences. Findings from these studies may lead to new insights and interventions targeting this high-risk group. Such findings reinforce the importance of implementing interventions targeting drug reduction as part of comprehensive and efficacious HIV prevention program.

→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIAID**, NIDA, NIMH)

National Epidemiologic Survey on Alcohol and Related Conditions: Predicting the First Use of Alcohol and Illicit Drugs and Correlated Brain Disorders: The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) collected comprehensive, detailed data from approximately 40,000 individuals on alcohol consumption, use of 10 categories of drugs, and symptoms of alcohol and specific drug use disorders, as well as mood, anxiety, and personality disorders in 2 separate waves. Results from the second wave of this nationally representative survey will provide predictors for the first incidence of substance abuse as well as mood and anxiety disorders. The rates of occurrence at 1 year of the survey were highest for alcohol abuse, alcohol dependence, major depressive disorder, and generalized anxiety disorder. The effects were much greater among men for substance use disorders and greater among women for mood and anxiety disorders, except for bipolar disorders and social phobia. African Americans were at decreased risk for alcohol abuse and Hispanic individuals were at decreased risk of generalized anxiety disorder. Substance abuse, mood disorders, and anxiety disorders occurred at similar or higher rates when compared to lung cancer, stroke, and cardiovascular disease. The higher incidence of all disorders in the youngest individuals highlights the need for increased vigilance in identifying and treating these disorders among young adults.

→ Grant BF, et al. *Mol Psychiatry* 2009;14(11):1051-66. PMID: 18427559. PMCID: PMC2766434.
→ (I) (**NIAAA**)

Building a Longitudinal Mental Health Tracking System: NIH has laid the initial groundwork to develop a mental health tracking system that will provide epidemiologic information on mental disorders on a continuing basis. By working with Federal agencies that currently conduct large-scale, ongoing national surveys, and adding detailed measures of mental health status, functioning, and service use, NIH will leverage existing resources to collect important mental health information in a cost-efficient manner. The longitudinal nature of the resulting data will provide NIH the ability to track the prevalence, incidence, severity, correlates, and trajectories of mental disorders, as well as related service use and outcomes, over time. The resulting data also could provide important information on key subgroups (e.g., racial/ethnic populations, people with autism) and geographic areas of varying sizes (e.g., states, counties). These data are critical for targeting future research activities and ensuring the effectiveness of delivered interventions.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIMH**)

The National Children's Study (NCS): NCS promises to be one of the richest information resources available for answering questions related to children's health and development and will form the basis of child health guidance, interventions, and policy for generations to come. The landmark study will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. This extensive research effort will examine factors ranging from those in the natural and man-

made environment to basic biological, genetic, social, and cultural influences. By studying children through their different phases of growth and development, researchers will be able to understand better the role of these factors in both health and disease. Specifically, the NCS will identify factors underlying conditions ranging from prematurity to developmental disabilities, asthma, autism, obesity and more. The study is led by a consortium of Federal agencies including NIH, CDC, and the EPA.

→ For more information, see http://www.nationalchildrensstudy.gov
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (I) (**NICHD**, NIEHS)

Fetal Alcohol Effects: The developing embryo and fetus is very vulnerable to the adverse effects of alcohol. Since Fetal Alcohol Syndrome was first recognized around 1970, NIH has supported research on outreach to pregnant women for identification and intervention of risky drinking; research to enhance our ability for early identification of and interventions with prenatal alcohol-affected children; research exploring nutritional and pharmacological agents that could lessen alcohol's adverse effects on the developing embryo/fetus; and research on how alcohol disrupts normal embryonic and fetal development. For example, a recent study with rats showed that choline, an essential nutrient, was found to effectively reduce the severity of some fetal alcohol effects, even when administered after the ethanol insult was complete. NIH also is investing in a large-scale prospective study looking at prenatal alcohol exposure along with other maternal risk factors in adverse pregnancy outcomes. Following a 3-year feasibility study, NIH established the Prenatal Alcohol, Sudden Infant Death Syndrome, and Stillbirth (PASS) Research Network, a multidisciplinary consortium to determine the role of prenatal alcohol exposure and other maternal risk factors in the incidence and etiology of sudden infant death syndrome (SIDS), stillbirth, and fetal alcohol syndrome, all of which are devastating pregnancy outcomes. The PASS study prospectively will follow 12,000 pregnant, high-risk, American Indian and South African women and their infants until the infants are 12 months old. Maternal, fetal, and infant measures and tissues will be obtained for analysis.

→ For more information, see http://www.nichd.nih.gov/research/supported/pass.cfm
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIAAA, NICHD**)

Strategies to Manage and Prevent Food Allergies: Food allergy occurs in approximately 4.7 percent of children under 5 years of age and in 3.7 percent of children 5 to 17 years of age. Allergies to peanuts and tree nuts, the allergens most relevant to severe food allergy and anaphylaxis, occur in approximately 1 percent of children and adults. Severe whole-body allergic reactions, also known as anaphylaxis, are a frequent cause of emergency room visits, many of which are attributed to food allergy. Every year in the United States, it is estimated that there are approximately 15,000-30,000 episodes of food-induced anaphylaxis. NIH seeks to understand better both the immune system response to food allergies and how certain foods trigger an allergic reaction. Researchers in the United States and abroad are conducting clinical trials to improve management of allergy to cow's milk, egg, and peanut, and innovative clinical trials are assessing strategies to prevent development of peanut allergies. One important trial will determine whether early and regular consumption of a peanut snack by infants and very young children at risk of developing peanut allergy will promote tolerance and prevent the development of this allergy. In FY 2008, NIH sought to bring new investigators into the field through the Exploratory Investigations in Food Allergy initiative, which supports innovative pilot studies and developmental research on the mechanisms of food allergy. The program will be recompeted in FY 2010. During this period, NIH continued funding for the Consortium of Food Allergy Research, which supports basic, preclinical, and clinical research to assess the pathophysiology and natural history of food allergy-associated anaphylaxis and to develop interventions to prevent and treat food allergy.

→ For more information, see http://www3.niaid.nih.gov/topics/foodAllergy/default.htm

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAID**)

Eye Disease Burden Data from National Health and Nutrition Examination Survey (NHANES): The CDC uses rigorous national surveys such as NHANES to collect information on the health of the U.S. population. In 1999, NIH and CDC collaborated to add estimates of vision impairment to NHANES. Based on an analysis of baseline NHANES data from 1999-2004, it was estimated that half of the U.S. population over the age 20 years has blurry vision, called refractive errors (nearsightedness, farsightedness, and/or astigmatism). Refractive errors can be corrected with eyeglasses, contact lenses, or surgery to restore clear vision. After 2004, a new survey was developed to capture information on more severe visual impairments, the extent of uncorrected (but correctable) refractive errors, the methods individuals selected to correct refractive error, and vision-related quality-of-life questions. These changes will improve estimates of the extent and nature of vision impairment in the United States. The effort to develop visual impairment statistics is consistent with an NIH GPRA goal to "develop stable national estimates of vision impairment by extending the vision component of NHANES."

→ Vitale S, et al. *Arch Ophthalmol* 2008;126(8):1111-9. PMID: 18695106. PMCID: PMC2772054.
→ For more information, see http://archopht.ama-assn.org/cgi/content/full/126/8/1111
→ For more information, see http://www.cdc.gov/nchs/nhanes.htm
→ (I, O) (**NEI**) (GPRA)

End-Stage Renal Disease: According to the United States Renal Data System—an NIH-supported national data system that collects, analyzes, and distributes information about people with kidney failure—more than one-half million Americans suffer from kidney failure. Patients with this condition—known as end-stage renal disease or ESRD—require a kidney transplant or hemodialysis, a process that uses a machine to remove waste products and excess fluid from the bloodstream. To facilitate hemodialysis, some patients undergo a surgical procedure to create a site on the body that allows easy, repeated access to the blood vessels. However, over time, many vascular access sites become unusable and fail. The NIH-supported Dialysis Access Consortium found that treatment with an anti-blood clotting drug did not improve the long-term suitability of a type of access known as a fistula. A separate study by the consortium found that the long-term usability of a different type of access site, known as a graft, could be improved through treatment with a combination of aspirin and another anti-clotting drug. Still, important questions remain. To better understand the underlying biology of access site maturation, NIH is launching a Vascular Biology of Hemodialysis Vascular Access Consortium to study the molecular and cellular pathways that contribute to vascular injury and high rates of vascular access failure. Such research may inform new strategies to improve outcomes in patients undergoing hemodialysis.

→ Dember LM, et al. *JAMA* 2008;299(18):2164-71. PMID: 18477783.
Dixon BS, et al. *New Engl J Med* 2009;360(21):2191-201. PMID: 19458364.
→ For more information, see http://www.usrds.org
→ For more information, see http://www.nih.gov/news/health/may2008/niddk-22a.htm
→ For more information, see http://www.nih.gov/news/health/may2009/niddk-20.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDDK**)

Research on Bariatric Surgery: The multicenter NIH-funded Longitudinal Assessment of Bariatric Surgery (LABS) consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Results from this study have been published in the *New England Journal of Medicine*. The study also addresses comparative effectiveness with respect to its collection of data on surgical procedures and pre- and post-operative information. Because bariatric surgery also is used in clinical practice sometimes as a treatment for severely obese adolescents,

NIH additionally is supporting an observational study of teens already scheduled for surgery, Teen-LABS, to collect data to help determine whether it is an appropriate treatment option for extremely obese adolescents. A pilot study also is being conducted using the new Metabolic Clinical Research Unit at the NIH CC to examine changes in insulin resistance after bariatric surgery. To further explore the observation that certain bariatric surgical procedures are associated with amelioration of obesity-related insulin resistance and diabetes soon after surgery, and thus independent of weight loss, NIH issued a funding opportunity announcement to encourage research in this area.

→ Adams TD, et al. *N Engl J Med* 2007;357(8):753-61. PMID: 17715409.
The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. *N Engl J Med* 2009;316(5):445-54. PMID: 19641201.
→ For more information, see http://win.niddk.nih.gov/publications/labs.htm
→ For more information, see http://www.nih.gov/news/pr/apr2007/niddk-16.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIDDK**, ORWH)

The Hispanic Community Health Study: In October 2006, NIH began the largest long-term epidemiological study of health and disease ever conducted in people of Hispanic/Latino heritage living in the United States. The study includes 16,000 participants of diverse Hispanic/Latino background, including Mexican, Cuban, Puerto Rican, and Central/South American. It is designed to identify factors that render these groups either susceptible to or protected from heart disease, stroke, asthma, chronic obstructive pulmonary disease, sleep disorders, dental disease, hearing loss, diabetes, kidney and liver disease, cognitive impairment, and other chronic conditions. Recruitment started in March 2008 in four cities. Variables such as height, weight, and other body measurements; blood pressure; blood lipids and glucose levels; diet; physical activity; smoking; acculturation; socioeconomic status; psychosocial factors; occupational history and exposure; access to and use of health care services; and use of medications and dietary supplements currently are being assessed.

→ For more information, see http://www.cscc.unc.edu/hchs
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NHLBI**, NCMHD, NIDCD, NIDCR, NIDDK, NINDS, ODP/ODS)

The Multi-Ethnic Study of Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter epidemiological study of cardiovascular disease (CVD) in 6,914 men and women from 4 ethnic groups—white, African-American, Hispanic, and Chinese—who have been followed for almost 10 years to identify predictors of progression of subclinical CVD. The study originally was funded from 1999 to 2008 and subsequently renewed through 2015. It has measured and compared the predictive value of chest computed tomography, cardiac magnetic resonance imaging, carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for the development of CVD. MESA has major ongoing ancillary studies in the areas of air pollution (funded by the EPA), chronic lung disease, and genetics. MESA SHARe (SNP Health Association Resource) will combine genome-wide scans with detailed phenotypic information and share these data with the scientific community for genome-wide association analyses.

→ For more information, see http://mesa-nhlbi.org
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Genomics*
→ (E) (**NHLBI**, NEI)

Culture of Cooperation to Promote Public Health

Research Initiatives to Study Suicidality and Mental Health Needs of U.S. Army Soldiers and Returning Combat Veterans: The high rates of mental health and behavioral adjustment problems among recent U.S. military combat veterans, and the increasing rates of suicide among Army soldiers, are of growing concern. To address these issues, NIH is collaborating with the U.S. Army to evaluate selected groups of soldiers across all phases of Army service, including entry-level training and service, pre-deployment training, deployment and noncombat assignments, post-deployment, and post-separation reintegration to civilian life. The study's intent is to identify modifiable risk and protective factors, as well as moderators, of suicide-related behaviors. NIH also is launching a study of the impact of existing national, state, and local community-based programs addressing the adjustment and mental health needs of recent combat veterans, including returning National Guard, Army Reserve, and newly separated active duty personnel. This initiative will produce new information concerning effective strategies for fostering successful transition from combat to civilian roles for returning service members.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-140.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-070.html
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIMH**)

Diabetes and Pesticide Exposure/the Agricultural Health Study: Exposure to certain pesticides increased the risk of diabetes in licensed applicators, according to researchers from NIH. The investigation of applicators enrolled in the Agricultural Health Study is the largest study to date to evaluate potential effects of pesticides on diabetes incidence in adults. Because previous studies using data from the National Health and Nutrition Examination Survey (NHANES) found associations of diabetes with serum levels of persistent organic pollutants, the researchers wanted to know if there was a similar association between diabetes and lifetime exposure to pesticides. Therefore, they evaluated applicators who reported diabetes for the first time in 5-year follow-up telephone interviews, conducted between 1999 and 2003. Previously, applicators had described use of 50 different pesticides, providing information on 2 primary measures: ever use and cumulative lifetime days of use. Of 50 pesticides evaluated, 7 were associated with an increased incidence of diabetes using both exposure measures. Three of these were organochlorine insecticides (aldrin, chlordane, heptachlor), 2 were organophosphate insecticides (trichlorfon, dichlorvos), and 2 were herbicides (alachlor, cyanazine). The strongest association was with trichlorfon: Applicators who had used the chemical on more than 10 days in their lifetime had a 2.5-fold increase in risk. Pesticide applicators who reported exposure to these pesticides showed an increased risk of diabetes independent of age, state of residence, and body mass index. The increasing burden of diabetes in populations worldwide warrants an improved understanding of the possible relation of diabetes risk to long-term, low levels of pesticide exposure.

→ Montgomery MP, et al. *Amer J Epidemiol* 2008;167:1235-46. PMID: 18343878.
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E/I) (**NIEHS**, NCI)

EARLI, the Early Autism Risk Longitudinal Investigation: EARLI, the Early Autism Risk Longitudinal Investigation, comprises a network of leading autism researchers from three regions across the country. EARLI is following a cohort of 1,200 mothers of children diagnosed with autism who are pregnant or planning a pregnancy. The EARLI network will study how genetics and environmental factors work together to cause autism by studying families who already are affected by autism. Data will be collected prospectively via clinical assessment, interviews, self-reports, medical record review, home environment assessments, and biologic samples that will be used in current analysis and stored for future studies. Planned analyses include a determination of whether in utero exposure to organic pollutants such as polychlorinated biphenyls (PCBs), brominated diphenyl ethers (BDEs), and persistent organic pollutants (POPs) is associated with autism risk.

→ For more information, see http://earlistudy.org
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIEHS**)

Addressing Drug Abuse and Comorbidities in Returning Vets and Their Families: Sustained U.S. combat operations in Afghanistan and Iraq have resulted in military personnel experiencing increased numbers and lengths of deployments and greater exposure to traumatic stressors. Stress can be a major contributor to both the onset and exacerbation of substance abuse and other mental health problems, and can lead to relapse in former substance abusers. To understand better the intervention needs of this group, NIH in 2009 sponsored a 2-day meeting to formulate a research agenda for conducting addiction prevention and treatment research with military and veteran populations and their families. Collaborators included the U.S. Army Medical Research and Materiel Command, the Department of Defense Health Affairs, the Army Center for Substance Abuse Programs, the Department of Veterans Affairs, and several NIH ICs. Subsequently, a call for studies on trauma, stress, and substance use and abuse among U.S. military personnel, veterans, and their families was issued. It focuses on epidemiology/etiology, screening and identification, and prevention and treatment of substance use and abuse—including alcohol, tobacco, and other drugs—and associated problems (e.g., PTSD, traumatic brain injury, sleep disturbances, and relationship violence) among U.S. military personnel, veterans, and their families. Further, NIH's National Drug Abuse Treatment Clinical Trials Network (CTN) is developing a protocol concept for the treatment of PTSD and drug abuse/dependence in veteran populations. It is expected that this study will be conducted in clinics participating in the CTN, which include some Veterans Administration hospitals and research facilities.

→ For more information, see http://www.drugabuse.gov/pdf/tib/veterans.pdf
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIDA**, NCI, NIAAA, NIMH)

Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer Care: The purpose of the Cancer Research Network (CRN) is to enhance research on cancer epidemiology, prevention, early detection, and control in the context of health care delivery systems. CRN combines established research groups affiliated with 14 health care delivery organizations that provide comprehensive care to a racially and ethnically diverse population of nearly 11 million individuals. CRN has developed strong research capabilities in several areas: developing and applying innovative methods to collect and interpret data from both conventional and electronic medical records systems; assembling large samples of patients with documentation of patient characteristics and longitudinal data on receipt of health services and clinical and quality-of-life outcomes; collecting and integrating complex data from patients, providers, and organizations to examine issues in health care delivery from multiple perspectives; quantifying the effect of key factors in the delivery process that may determine quality and outcomes of care; and conducting studies on behavioral and systems-based interventions to improve the delivery of care in community-based health care delivery systems. The Breast Cancer Surveillance Consortium (BCSC) is a research resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. The BCSC is a collaborative network of seven mammography registries with linkages to tumor and/or pathology registries. The Consortium's database contains information on 7,521,000 mammographic examinations, 2,017,869 women, and 86,700 cancer cases.

→ For more information, see http://crn.cancer.gov
→ For more information, see http://breastscreening.cancer.gov/
→ This example also appears in Chapter 2: *Cancer*, Chapter 3: *Clinical and Translational Research* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**NCI**)

Population Genomics, GAIN, and GEI: In 2006, HHS announced the creation of two groundbreaking initiatives for population genomics research in which NIH played a leading role. The Genetic Association Information Network (GAIN) was a public-private partnership involving NIH, the Foundation for NIH, Pfizer, Affymetrix, Perlegen, the Broad Institute, and Abbott. GAIN supported a series of genome-wide association studies designed to identify specific points of DNA variation associated with the occurrence of common diseases. Investigators from existing clinical studies were invited to submit samples and data on roughly 2,000 participants for genomic assays designed to capture roughly 80 percent of the common changes in the human genome. GAIN successfully concluded in November 2008, with the third and final public workshop on the project. At this meeting, investigators from across the research community shared their findings and discussed how they had used the data generated through GAIN in their own research. Data from the GAIN studies have been deposited into the NIH database of Genotype and Phenotype (dbGaP) for the broad use of the research community. Access is controlled by the GAIN Data Access Committee. Additionally, NIH funds the Genes, Environment, and Health Initiative (GEI), an NIH-wide effort combining comprehensive genetic analysis and environmental technology development to understand the causes of common diseases. GEI has held a number of workshops to identify novel ways of analyzing the wealth of information gathered and to use that data to improve human health.

→ For more information, see http://www.genome.gov/19518664
→ For more information, see http://www.genome.gov/19518663
→ For more information, see http://genesandenvironment.nih.gov
→ For more information, see http://www.genome.gov/11511175
→ This example also appears in Chapter 3: *Genomics*
→ (E, I) (**NHGRI**, NIEHS, NLM)

Urology Research: The Urinary Incontinence Treatment Network (UITN) conducts long-term studies and clinical trials of the most commonly used surgical, pharmacological, and behavioral approaches for management of urinary incontinence in women diagnosed with stress and mixed incontinence. Recently, a different group of investigators completed the Program to Reduce Incontinence by Diet and Exercise (PRIDE) study and determined that a weight loss program could reduce significantly the frequency of urinary incontinence in overweight and obese women. Several studies address interstitial cystitis/painful bladder syndrome (IC/PBS), a urologic condition whose prevalence is uncertain and which remains difficult to diagnose and treat. The RAND Interstitial Cystitis Epidemiology (RICE) study is designed to estimate the prevalence of interstitial cystitis and establish a working definition of this condition. The Boston Area Community Health (BACH) Survey is a population-based study of urologic conditions, including IC/PBS, in more than 5,500 adults. Results emerging from BACH about IC/PBS will provide a clearer picture on the IC/PBS burden in the population, and will inform research efforts to reverse this burden. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is designed to enhance understanding of the major urological chronic pelvic pain disorders, including IC/PBS and chronic prostatitis/chronic pelvic pain syndrome.

→ Burgio KL, et al. *Ann Int Med* 2008;149:161-9. PMID: 18678843.
Subak LL, et al. *N Eng J Med* 2009;360(5):481-90. PMID: 19179316.
→ For more information, see http://www.uitn.net/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**, NICHD)

According to a Government Survey, 38 Percent of Adults and 12 Percent of Children Use Complementary and Alternative Medicine: In December 2008, NIH and the National Center for Health Statistics released new findings on Americans' use of complementary and alternative medicine (CAM). The findings are from the 2007 National Health Interview Survey (NHIS), an annual in-person survey of Americans regarding their health- and illness-related experiences. According to the survey, approximately 38 percent of adults and nearly 12 percent of children use some form of CAM. For

both adults and children, the most commonly used type of CAM is nonvitamin/nonmineral natural products, and the most common use for CAM is to treat pain. Although overall use of CAM among adults has remained relatively stable since 2002 (the last time NHIS included a CAM section), the use of some specific CAM therapies has varied substantially; for example, deep breathing, meditation, massage therapy, and yoga have all shown significant increases. The 2007 NHIS was the first to ask about CAM use by children. The NHIS also reports on characteristics of CAM users, such as gender, age, education, geographic region, poverty status, and health indicators. The 2007 NHIS provides the most current, comprehensive, and reliable source of information on Americans' use of CAM. These statistics confirm that CAM practices are a frequently used component of American's health care regimens, and reinforce the need for rigorous research to study the safety and effectiveness of these therapies. The data also point out the need for patients and health care providers to openly discuss CAM use to ensure safe and coordinated care. Future analyses of these data may help explain some of the observed variation in the use of individual CAM therapies and provide greater insights into CAM use patterns among Americans.

→ Barnes PM, et al. *Natl Health Stat Report* 2008;(12):1-23. PMID: 19361005.
→ For more information, see http://www.cdc.gov/nchs/data/nhsr/nhsr012.pdf
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NCCAM**, CDC)

Half of Surveyed Physicians Use Placebo Treatments for Patients: Treating patients with placebos has a long, complicated, and often controversial history. Nonetheless, little actually is known about U.S. physicians' current attitudes toward and use of placebo treatments. A national survey funded in part by NIH looked at placebo-prescribing practices among 679 internists and rheumatologists—specialties that commonly treat patients with debilitating chronic conditions. The survey found that about half of the physician respondents prescribed placebo treatments on a regular basis. Most (62%) said they think the practice is ethical. Among physicians who prescribed placebos, few said they used inert treatments such as saline injections or sugar pills; they were more likely to recommend over-the-counter analgesics (41%) or vitamins (38%), and some used antibiotics (13%) or sedatives (13%) as placebos. The survey also found that the physicians who used placebos rarely described them as such to patients. Instead, physicians most commonly described the treatments as medicine that typically is not used for the patient's condition but that might be beneficial. The survey provides insights into the complex relationship between placebo use and physicians' traditional role in promoting positive expectations in their patients. It also raises concerns about the use of "active" placebos, particularly antibiotics and sedatives, when they are not medically indicated. Prescribing placebo treatments remains an appropriate topic for ethical and policy debates.

→ Tilburt JC, et al. *BMJ* 2008 Oct 23;337:a1938. PMID: 18948346. PMCID: PMC2572204.
→ For more information, see http://nccam.nih.gov/research/results/spotlight/102408.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NCCAM**)

Study Shows One-Fifth of Internet-Available Ayurvedic Medicines Contain Toxic Metals: Ayurveda, a traditional medical system that originated in India, aims to integrate and balance the body, mind, and spirit to help prevent illness and promote wellness. Potentially toxic metals sometimes are incorporated in traditional Ayurvedic medicines as part of rasa shastra—a practice that combines herbs with metals, minerals, and gems. In an NIH-funded study, researchers sought to determine how often Ayurvedic medicines sold on the Internet contain detectable levels of lead, mercury, and arsenic. They purchased products manufactured in both India and the United States and examined both rasa shastra and nonrasa shastra (herbal-only) medicines. Using 5 different search engines, the researchers found 25 websites that sold traditional Ayurvedic herbs, formulas, and ingredients. Of the 230 products randomly selected for purchase, 193 were received and

tested for the presence of metals. Nearly 21 percent of the Ayurvedic medicines tested were found to contain detectable levels of lead, mercury, or arsenic. Rasa shastra products were more than twice as likely as nonrasa shastra products to contain metals, and several rasa shastra medicines manufactured in India could result in lead and/or mercury ingestion 100 to 10,000 times greater than acceptable limits. This study's findings lend support to the value and importance of rigorous standards of product quality and self-regulation within the herbal medicine and dietary supplement industry. The authors call for strictly enforced, government-mandated, daily-dose limits for toxic metals in all dietary supplements, and requirements that all manufacturers demonstrate compliance through third-party testing.

→ Saper RB, et al. *JAMA* 2008;300(8):915-23. PMID: 18728265. PMCID: PMC2755247.
→ For more information, see http://nccam.nih.gov/research/results/spotlight/082808.htm
→ (E) (**NCCAM**)

SNP-Health Association Resource (SHARe): SHARe conducts genome-wide association studies in several large NIH cohort studies to identify genes underlying cardiovascular and lung diseases and other disorders such as obesity and diabetes. The resulting genotype data along with the cohort phenotype data are made available to researchers around the world through the NIH dbGAP database. Framingham SHARe, with 9,000 participants, was the first cohort released in this initiative due to its uniqueness in including 3 generations of participants with comparable data obtained from each generation at the same age. As of October 31, 2009, 95 projects to use these data had been approved. A modified version of the dataset was distributed to 72 approved research projects as the focus of a Southwest Foundation Genetic Analysis Workshop. The second cohort released was the SHARe Asthma Resource Project, which includes genotype data from more than 2,500 adults and children who have participated in NIH clinical research trials on asthma. As of October 31, 2009, 11 projects to use these data had been approved. Data from more than 12,000 African-American and Hispanic women from the Women's Health Initiative and approximately 8,300 participants from the Multi-Ethnic Study of Atherosclerosis were released in January 2010.

→ For more information, see http://www.nih.gov/news/pr/oct2007/nhlbi-01.htm
→ For more information, see http://nih.gov/news/health/dec2008/nhlbi-15.htm
→ For more information, see http://view.ncbi.nlm.nih.gov/dbgap/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
→ (E) (**NHLBI**, NLM)

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Genomics

When the United States launched a massive effort to sequence the human genome in 1990, many said it could not—or should not—be done. Skeptics feared that the cost would be too high, draining funds from other, more promising research. They warned that adequate technology did not exist to complete the project, and that the cost of developing the necessary technology was unsupportable. Methods of sequencing DNA were barely past the laboratory-bench stage and cost about $10 for each base pair (bp); at that rate, sequencing a human genome would cost at least $30 billion. Moreover, the prevailing wisdom was that most of the genome was meaningless "junk" that could be ignored, rather than "coding areas"—the genes—that instruct cells in the body how to make proteins.

But one of the earliest goals of the Human Genome Project was to boost the speed and cut the cost of sequencing DNA. By 2004, newly developed technology could sequence a full genome for just $20 million. By 2009, even newer sequencing machinery could do the job for $100,000. Now, NIH is on track to achieve its goal of technology that can sequence an individual patient's DNA for $1,000—less than the price tag of some high-tech medical tests today—which will usher in a new era of medicine. (And along the way, scientists are learning that the "junk" is very important indeed.)

Introduction

Genomics is the study of an organism's entire genome—the complete assembly of DNA (deoxyribonucleic acid), or in some cases RNA (ribonucleic acid)—that transmits the instructions for developing and operating a living organism. Genomic research focuses not just on individual genes but also on the functioning of the entire genome as a network and, importantly, on how this network interacts with environmental factors to influence health and cause disease. Genomics is a new and challenging discipline that is increasingly used in virtually every field of biological and medical research.

DNA is made up of four chemical compounds called "nucleotides"—adenine, thymine, guanine, and cytosine—denoted by the letters A, T, G, and C respectively. These nucleotides are assembled in two parallel strands in the form of a double helix. Each nucleotide in one strand always links to the same partner on the other strand: A always pairs with T; C always pairs with G. Each of these pairings is referred to as a "base pair." The human genome consists of about 3 billion base pairs, packaged in 23 sets of chromosomes, wrapped extremely tightly into the nucleus of virtually every cell in the body. Identifying the base pairs—and thus the letters—and the order in which they appear on any stretch of DNA is called "sequencing" that segment.

DNA's double helical structure was discovered in 1953. The human genome was fully sequenced 50 years later, in 2003, by a 13-year, U.S.-led multinational effort called the Human Genome Project, which ended ahead of schedule and under budget. The sequencing of the human genome generated immense scientific excitement. It provided a new means of analyzing the functions of cells, tissues, and systems in the body and offered new tools for understanding the causes of disease. It laid the foundation for broad new scientific disciplines such as proteomics, the study of the structure and function of all the proteins produced by the body (in response to instructions carried by the genes). Recent studies have demonstrated that the genome contains more information than can be interpreted from just its sequence. It is more complex, more variable in its structure, and more complicated in its internal interactions than anyone imagined just a few years ago.

Almost every human disease or disorder has a genetic component and an environmental component. The genetic component for some heritable diseases, such as sickle cell disease or cystic fibrosis, result from mutations in single genes—changes that disrupt the function of the protein they encode. However, in most diseases the role of genes and the environment is more complicated. Some diseases arise as a result of spontaneous gene mutations that occur during a person's lifetime; others are caused by complex cascades of changes in gene expression triggered, perhaps, by environmental factors. Differences as small as one letter in our 3 billion pairs of DNA letters can cause disease directly or

make people respond differently to particular pathogens or drugs. Multiple genetic and environmental factors play a role in myriad common diseases, such as heart disease, cancer, and asthma, but for no common disease have all the genes involved yet been identified.

Educational resources, including multimedia presentation, to help the public understand genomics are available on the NIH website.

As a result of the overwhelming influence of the genome on human health, virtually every NIH Institute and Center now engages in genome-related research.

As a result of the overwhelming influence of the genome on human health, virtually every NIH IC now engages in genome-related research. Like many NIH Institutes, NCI supports a huge array of gene-oriented projects, including Genome-Wide Association Studies (GWAS)—in effect, full-body DNA scans—that recently detected new genetic factors involved in breast, prostate, and colon cancers. Over the past 2 years, NHLBI and NIGMS have sponsored a research consortium that combined both genetic and clinical data to devise a computer algorithm for setting the proper dose of the blood-thinner warfarin, commonly prescribed for heart patients and others.[14] A major clinical trial began in early 2009 to test whether that new algorithm is better than the current trial-and-error method. NIMH-supported researchers recently identified a stretch of DNA (on chromosome 6) that appears to be implicated in both schizophrenia and bipolar disorder—a finding that may aid the search for treatments and suggests that both disorders flow from errors in wiring the brain during fetal development, potentially opening a new line of research.[15, 16, 17] NIAID now has sequenced the genomes of thousands of infectious microorganisms, including 4,000 influenza viruses; within a few months of the emergence of the 2009 H1N1 influenza—the so-called "swine flu" virus—in early 2009, it had sequenced nearly 1,000 separate H1N1strains.

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NIH researchers and grant recipients also have increased the pace of sequencing other nonhuman genomes. Full sequences of nearly 200 organisms now have been completed or are underway, and not just the genomes of our close primate relatives such as the chimpanzee. Between 2007 and 2009, NIH-supported scientists completed sequencing the genomes of 16 invertebrates, 1 mammal, and the egg-laying duck-billed platypus—whose genome retains many reptilian features—and selected 34 new organisms for full-genome sequencing. Comparing the human genome to the genomes of other creatures, including insects and even single-celled organisms, reveals stretches of DNA that have remained similar over millions of years of evolution. These "conserved" sequences are thought to play an important role in the functioning of a living organism, even if scientists do not yet know what that role is.

Genes themselves, the "coding regions" of DNA that direct cells to make particular proteins, account for only about 2 percent of the human genome. Locating the noncoding but functional sequences throughout the rest of the genome is the main mission of the ENCODE research consortium (the acronym stands for **ENC**yclopedia **O**f **D**NA **E**lements). NIH also has pressed ahead with the Model ENCODE project (modENCODE) to identify all the functional elements in the genomes of two hugely important and widely used laboratory model organisms—the fruit fly *Drosophila melanogaster* and the roundworm *Caenorhabditis elegans*.[18] The strategy is that identifying genomic mechanisms in these model organisms will elucidate novel research directions for human genomic and other researchers. (Also see the section on *Molecular Biology and Basic Research* in Chapter 3.)

Approaching the Era of Personalized Medicine

DNA sequencing and analysis projects serve another purpose as well: advancement of technology and bioinformatics that may soon bring revolutionary improvements to the practice of medicine. The development of new methods to sequence DNA faster and more cheaply is the central goal of some NIH-sponsored projects, and as NIH has continued to fund technological innovation in this area, the costs have continued to fall remarkably. Soon, when a patient's full genome can be sequenced for less than the cost of other routine medical tests, and when ongoing genomic research programs have further broadened and deepened our understanding of the genome's functioning, medical science will stand on a new plateau. The practice of medicine will move beyond a one-size-fits-all approach—and the promise of personalized medicine will be realized. One application of personalized medicine is pharmacogenomics, which seeks to understand the inherited variations in genes that dictate drug response. Furthermore, it explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a poor or adverse response to a drug, or no response at all. By understanding the differences in the genetic basis of drug responses, scientists hope to enable doctors to prescribe the drugs and doses best suited for each individual. The mission of the NIH Pharmacogenetics Research Network (PGRN) is to better understand the genetic basis for variable drug responses and identify safe and effective drug therapies designed for individual patients.

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Most of the genome research that will yield direct clinical implications, improve our understanding of human health, and change clinical practice still lies ahead. However, over the next decade, research will unlock the true potential of this foundational work, leading scientists closer to better means for preventing, diagnosing, and treating disease.

Summary of NIH Activities

Among NIH's key activities and accomplishments in the field of genomics in FYs 2008-2009 were those involving the following:

- **New Genome-Wide Association Studies (GWAS)**. Using DNA from tissue samples, GWAS scan and compare entire genomes of people with and without a particular disease, looking for single-base differences (known as single nucleotide polymorphisms, or SNPs) that might signal the presence of a gene or some other functional sequence implicated in the disease. GWAS are based on the Haplotype Map (HapMap) of the human genome, produced via an NIH-led international research team earlier in the decade that identified more than 3 million relatively common SNPs in human genomes that serve as markers for larger neighborhoods of DNA sequences. GWAS scans point to regions of the genome that are worthy of closer study in seeking the genetic cause of a disease. Hundreds of such studies have been conducted since the technique was first developed in 2005, flagging genetic areas that may be linked with at least 80 different diseases and disorders including heart disease, diabetes, obesity, and many types of cancer. In 2008 alone, GWAS identified more than 130 genetic factors involved in human disease. Among the GWAS currently under way is an effort to determine the genes involved in HIV disease progression and susceptibility to HIV acquisition.
- **The 1,000 Genomes Project**. This international research consortium assembled and led by NIH began sequencing the genomes of at least 1,000 people to improve dramatically on the current HapMap. The HapMap pinpoints DNA variations that are present in 5 percent or more of humans. The 3-year, 1,000 Genomes Project will achieve a finer resolution, creating a catalog of variations that are present in as few as 1 percent of people. It will focus even more tightly on the coding regions of genes, locating variations that are present in as few as 0.5 percent of individuals. Importantly, the new project will catalog not just SNPs but also structural variations in human DNA, such as deletions, duplications, and rearrangements of DNA sequences.
- **Structural variation**. Scientists have gathered increasing evidence that the genome is not a string of independently operating genes, but rather is a hugely complicated, integrated whole, and that variations in the structure of the chromosomes have a major impact on human health. Yet, the mechanisms involved are not fully understood. In 2008, an NIH-supported research consortium produced the first sequence-based map of large-scale structural variations,

ranging from a few thousand bases to several million.[19] These include deletions of whole genes, repetitions of sequences (sometimes multiple repetitions), and rearrangements of stretches of DNA. Some variants already have been linked to diseases, such as coronary heart disease, schizophrenia, and autism, and to differences in susceptibility to HIV infection.

- **New disease genes**. NIH researchers have identified individual genes or regions of DNA associated with, among other diseases and disorders: schizophrenia and bipolar disorder; cancers of the skin, lung, brain, pancreas, breast, prostate, and testicle, and acute lymphoblastic leukemia; diabetes; periodontitis in African Americans; asthma; high blood pressure; heart arrhythmias; Crohn's disease; obesity; and many others.
- **Clinical genomics**. NIH began a large pilot project to test ways that high-throughput genome sequencing might be used in a clinical setting for diagnosing and treating patients. Using the NIH Clinical Center, the trial, dubbed "ClinSeq" (for **clin**ical **seq**uencing) will enroll an initial 1,000 patients with a spectrum of coronary artery calcification from normal to diseased and will sequence 200 to 400 areas of their DNA that contain genes suspected of involvement in heart disease. Patients will have the option of learning the outcome of their tests, and those who carry a variant of a gene that has been linked to disease will be counseled and followed up, possibly for years. The study is designed both as a pilot project to explore ways of using genome sequencing in patient treatment and as an effort to develop new data about particular genes' involvement in heart disease. The project may expand in its later stages to cover other diseases.
- **Consumer interest**. ClinSeq is not the only way that NIH is exploring whether people want to know what genomics might have to tell them. In a program known as the Multiplex Initiative, individuals ages 25 to 40 are offered free testing for 15 genes associated with higher risk for type 2 diabetes, heart disease, high cholesterol, high blood pressure, osteoporosis, lung cancer, colorectal cancer, and malignant melanoma. Those who are offered the testing use an interactive, Internet-based program designed by NIH researchers that helps participants ask questions about the genetic testing, get information, and decide whether to receive the testing. Meanwhile, Multiplex Initiative researchers monitor the participants' decision process every step of the way. Those who decide to submit blood samples for the tests will be followed for some time afterward to see whether they change their behavior (for example, by adopting a healthier lifestyle or diet) in response to their test results.[20] Researchers involved with this study have found that individuals who discuss their genetic information with their doctors may be among the most motivated to take steps toward more healthy choices.
- **Pharmacogenetics**. NIH launched a major clinical trial to test a gene-based method of prescribing warfarin, a blood thinner that is widely used to prevent life-threatening blood clots. About 2 million Americans start taking warfarin each year, but the drug's effect on individual patients is notoriously variable. Regular blood tests are needed both to establish an initial dose level and to maintain the proper level as time goes on—for months and often for years. In early 2009, an international research consortium combined patients' genetic and clinical data to produce a computer algorithm that appeared to be more accurate than basing the initial dose on a patient's clinical condition alone and then increasing or decreasing the dose to achieve the optimal blood level.[1] NIH quickly began a multicenter clinical trial, known as the Clarification of Optimal Anticoagulation through Genetics (COAG) trial, to compare the gene-based method with the current trial and error approach in a much wider pool of patients. COAG will enroll 1,200 patients of varying backgrounds at 12 sites and will follow them for 6 months. Its outcome could improve protection against heart attacks and strokes for millions of Americans.
- **Nonhuman genomes**. NIH completed full sequencing and analysis of multiple vertebrate and invertebrate animal genomes in 2008-2009. These include the platypus, domestic cattle, the wasp, other insects, and a large number of disease-causing organisms—such as the malaria-causing parasite *Plasmodium vivax*, the common intestinal parasite *Giardia lamblia*, the Lyme disease-causing tick *Ixodes scapularis*, and two species of the parasitic flatworms that cause schistosomiasis. Also sequenced were thousands of separate strains of the constantly changing human influenza viruses. Molecular comparisons of the 2009 H1N1 influenza and other flu strains may help scientists learn how 2009 H1N1 is evolving, how it is interacting with other strains, and whether it is gaining or declining in virulence.
- **Health Disparities**. NIH-funded analysis of genomic data from 121 African populations, 4 African American populations, and 60 non-African populations revealed that all African populations descended from 14 ancestral groups. Most African Americans trace the majority of their ancestry to West Africa, a finding that will improve scientists' ability to identify genetic risk factors in African and African American populations.

Identifying Microbial Free-Riders: The Human Microbiome Project

Among the newer NIH initiatives is the 5-year Human Microbiome Project (HMP), an NIH-led international undertaking that seeks to identify and sequence the vast populations of microbes that live on and within the human body. Some scientists estimate that microbial cells outnumber human cells in a healthy adult by 10 to 1, but few of these fellow travelers have been characterized, and their role in human health largely is a mystery. Many, if not most, of these microbes cannot be grown in a laboratory dish; they are dependent on their natural environment—us. Therefore, to sequence their genomes, HMP researchers will use a new method called metagenomics, which involves sequencing and analysis of genetic material drawn from whole microbial communities in their natural setting.

Among the newer NIH initiatives is the 5-year Human Microbiome Project, an NIH-led international undertaking that seeks to identify and sequence the vast populations of microbes that live on and within the human body.

Initially, the project plans to analyze more than 250 samples from five human body sites—the skin, mouth, airways, gastrointestinal tract, and vagina—and produce a reference set of 1,000 microbial genomes. These will serve as a benchmark against which to compare further sequence data. The project also will test whether metagenomics can be used to link changes in the microbiome with human health.

In one early result from HMP, NIH researchers reported in May 2009 that human skin plays host to an even wider array of bacteria than anticipated.[21] Drawing on just 20 skin sites from 10 volunteers, the researchers found more than 112,000 bacterial gene sequences representing 19 phyla, 205 genera, and great species diversity. The widest variety of microbes roams the forearm, with 44 species there on average. The least populated site is behind the ear, with 19 species. The major determinant of what bacteria live where seems to be the same factor that governs human real estate prices: location, location, location. Bacteria from any particular body site are more like bacteria from that site in other people than to bacteria elsewhere on the original donor's body. In other words, donor A's mouth bacteria are more like other people's mouth bacteria than they are to bacteria living on donor A's forearm.

Findings such as these will be useful, of course, in developing new treatments for many human diseases. For instance, the study may contribute to efforts to control methicillin-resistant *Staphylococcus aureus* (MRSA), a dangerous bacterium that is resistant to current antibiotics and thus is a growing threat to human health. Scientists had known that many people harbored *S. aureus* in their nostrils; the HMP study detected very similar microbial communities in the crease of skin outside the nose, offering new clues about how the virus is spread, and possibly offering new approaches to preventive measures.

Decoding Cancer

Genomics research has moved the battle against cancer into new, exciting territory. In FY 2008 and FY 2009, GWAS led to the detection of new genes or DNA regions associated with a variety of human cancers. In addition, sequencing of the abnormal DNA within tumors provided new clues about cancer development and potential treatment.

NIH supports a wide variety of such studies, including: the Cancer Genetic Markers of Susceptibility (CGEMS) project, which has been expanded from an initial study of breast and prostate cancer; the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program, which uses genomics in an effort to develop treatments for childhood cancers; and The Cancer Genome Atlas (TCGA), which sequences the DNA within tumors and is being expanded because of the success of its original pilot stage.

Overall, more than 100 genetic variations associated with cancer risk now have been identified. Among the discoveries in FY 2008 and FY 2009 were: a link between pancreatic cancer and the gene that determines ABO blood type;[22] identification of a gene that appears to increase the risk of relapse in children treated for acute lymphoblastic leukemia;[23] and variations within several DNA regions that appear to raise the risk of breast,[24] colorectal,[25] and prostate cancers[26]—

including, intriguingly, one stretch that contains no genes at all, but that may contain a regulatory sequence that controls a faraway gene (or genes), and may suggest a novel mechanistic pathway of cancer susceptibility shared by a variety of cancers involving this region.

More than 100 genetic variations associated with cancer risk now have been identified.

Sequencing the scrambled DNA within tumors has led to additional discoveries. In one-fourth of melanoma tumors, a gene known as MMP was damaged, indicating that MMP is a tumor suppressor and opening a new approach to treatment of melanoma and other cancers.[27] Analysis of glioblastomas (a form of brain tumors) uncovered three disrupted genes and several damaged molecular pathways, suggesting an explanation of why some glioblastomas are resistant to chemotherapy.[28] Sequencing of tissue from lung adenocarcinomas, the most common form of lung cancer, detected 26 frequently mutated genes, more than doubling the number of genes linked to the disease.[29] Tumor sequencing has proved so fruitful that NIH has plans underway to carry out similar comprehensive analyses of 20 to 25 different cancer subtypes.

The rich lode of data produced by large-scale genomics studies in FY 2008 and FY 2009 may reveal yet more secrets. Much of the raw data is still being analyzed. Moreover, in late 2009, NIH held a workshop involving its own intramural researchers, university researchers, and private-sector officials to discuss the next steps: how to go about combining and analyzing the different data sets being produced, and how to cope with the flood of new data that is being produced as technology improvements make large-scale sequencing faster and cheaper. The advent of massively parallel sequencing technologies has opened an extensive new vista of research possibilities—elucidation of the human microbiome, discovery of polymorphisms and mutations in individual genomes, mapping of protein-DNA interactions, and positioning of nucleosomes—to name just a few. To store, access, and manipulate the enormous volume of read data generated from massively parallel sequencing experiments, NIH has created the Sequence Read Archive, which already contains more than 8,000 billion bases of DNA data.

Revolution in Technology

When the Human Genome Project was first conceived, the cost of sequencing DNA was about $10 per base pair, and the process was hands-on and painfully slow. If the technology had not been improved and automated, sequencing the genome would have taken more than 100 years and been impossibly expensive. As recently as 2004, the cost of sequencing a person's genome with the then-existing technology would have been about $20 million. That year, NIH adopted the Advanced DNA Sequencing Technology program and set a target of reducing the cost of sequencing a human genome to about $100,000 in 2009 and to just $1,000 in 2014. The goal of a $100,000 genome was achieved in 2009; the drive toward a $1,000 genome is on track. That is comparable to the cost of many high-technology medical tests and would make individual genome sequencing tests feasible for hospital patients, ushering in—or at least opening the door to—the era of personalized medicine.

Through the Advanced DNA Sequencing Technology program NIH set a target of reducing the cost of sequencing a human genome. The goal of a $100,000 genome was achieved in 2009; the drive toward a $1,000 genome is on track for 2014.

The speed of sequencing also is being dramatically accelerated. Although producing the first full human genome sequence took 13 years and required an international consortium of many laboratories, by 2009 the job could be done in a few weeks on a single sequencing machine. The latest sequencing machines can achieve three times the throughput of the most recent previous platforms, and sequencing capacity is expected to continue growing exponentially. Moreover, the new technologies can detect not just single base changes but also structural variations—rearrangements, duplications, and deletions. The capacity for full genome sequencing is now a possibility for any research laboratory.

A 2009 NIH workshop concluded that these rapid gains in sequencing technology, encouraged and in many cases funded by NIH, will yield a flood of new data to analyze, on top of a data stream that is already testing the limits of current analytic abilities. Improved technology spurs new applications of genomic science. Bioinformatics—that is, computational biology methods, resources, and infrastructure—is a critical tool for the understanding of this wealth of data.[30] This is a tremendous challenge, and opportunity, for 2010. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.)

We look toward a future where individual genome sequencing will become both commonplace and affordable, and where primary care physicians will routinely consult their patients' genome analyses for predictions of risk, diagnosis, and drug and dosage selections. As we educate the public and the medical community about the significance and limitations of genomic information, it will be possible to apply genomic knowledge to lessen the burden of disease through better screening, diagnostic, therapeutic, and prevention programs. (Also see the section on *Ensuring Responsible Research* in Chapter 3.)

Notable Examples of NIH Activity

Key
E = Supported through **E**xtramural research I = Supported through **I**ntramural research O = **O**ther (e.g., policy, planning, or communication) COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct IC acronyms in **bold** face indicate lead IC(s).

Functional Genomics of Disease

Medical Sequencing: As more is learned about the genetic contributions to disease, DNA sequence information will become even more important for providing medically relevant information to individuals and their health care providers. When it becomes practical to sequence each patient's genome, genetic information will be used to provide more individualized outlooks of disease risk and improve the prevention, diagnosis, and treatment of disease. NHGRI's medical sequencing program, initiated in 2006, aims to drive continued improvement in DNA sequencing technologies and to produce data important to biomedical research. Seven studies currently are underway to identify the genes responsible for several relatively rare disorders and to survey the range of gene variants that contribute to certain common diseases.

→ For more information, see http://www.genome.gov/15014882
→ This example also appears in Chapter 3: *Technology Development*
→ (E, I) (NHGRI)

Genomic Medicine: One of the promises of the Human Genome Project is the personalization of medicine. The time rapidly is approaching when health care providers will be able to use information about each person's unique genetic makeup to develop individualized strategies for detecting, treating, and, ultimately, preventing disease. A number of initiatives are underway to explore this area, including the Multiplex Initiative, the Surgeon General's Family History Initiative, and the ClinSeq project. The Multiplex Initiative, a collaboration between NIH researchers, the Group Health Cooperative in Seattle, and the Henry Ford Health System in Detroit, studied the interest levels of healthy young adults in receiving genetic testing for eight common conditions. The purpose was to understand better how patients respond to the results of genetic tests. The U.S Surgeon General's Family History online tool, created through a collaborative effort

involving the Office of the Surgeon General, NIH, the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, and the Health Resources and Services Administration, allows people to record health conditions that have affected their relatives. The tool uses a three-generation pedigree to organize family health information in a format that people can easily share with their health care providers and other family members. Such information can lead to more proactive strategies for preventing disease and improving health. Finally, NIH researchers and their collaborators are enrolling volunteers in the ClinSeq project, which is piloting large-scale medical sequencing in a clinical setting, with a focus on cardiovascular disease.

→ Guttmacher AE, et al. *N Engl J Med* 2004;351(22):2333-6. PMID: 15564550.
→ For more information, see http://www.multiplex.nih.gov
→ For more information, see http://www.genome.gov/25521052
→ For more information, see http://www.hhs.gov/familyhistory
→ For more information, see https://familyhistory.hhs.gov
→ For more information, see http://www.genome.gov/20519355
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E, I) (**NHGRI**)

Developmental Genomics: Neural tube defects are a class of birth defects affecting the brain and spinal cord. Taking folic acid during the weeks before and after conception greatly can reduce a woman's chances of having a child with a neural tube defect. Still, researchers have not yet fully defined the complex relationship that exists between folic acid and vitamin B12, which is essential for synthesizing DNA during growth and development. Because Ireland has a particularly high rate of neural tube defects, NIH researchers collaborated with Irish researchers to look more closely at the role of vitamin B12 in the developmental disorder. They found that children born to women who have low blood levels of vitamin B12 shortly before and after conception have an increased risk of a neural tube defect. In light of their discovery, researchers said it would be wise for all women of childbearing age to consume the recommended amount of vitamin B12 in addition to folic acid. In a study looking at a different type of birth defect, a trans-NIH team found that about 20 percent of the incidence of isolated cleft lip may be due to a very tiny alteration in a gene involved in facial development. Oral-facial clefts are among the most common birth defects in the United States, arising from disruptions in a dynamic but still poorly understood interplay of genes, diet, and environment.

→ Molloy AM, et al. *Pediatrics* 2009;123(3):917-23. PMID: 19255021.
Rahimov F, et al. *Nat Genet* 2008 Nov;40(11):1341-7. PMID: 18836445. PMCID: PMC2691688.
→ For more information, see http://www.genome.gov/27530477
→ For more information, see http://www.genome.gov/27528380
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E, I) (**NHGRI**, NICHD, NIDCR)

Study Finds Unexpected Bacterial Diversity on Human Skin: One of the NIH Roadmap initiatives, the Human Microbiome Project (HMP) is a trans-NIH program that aims to expand upon traditional microbiology and discover what microbial communities exist in different parts of the human body and how they might change with disease. In a healthy adult, microbial cells far outnumber those of the human host, but remarkably little has been known until now about how these microbes behave in the body. HMP makes use of a metagenomic approach that reveals data about entire human-associated microbial communities. In 2009, data gathered by a trans-NIH team revealed unexpected bacterial diversity on human skin that, it is hoped, will lead to advances in understanding a range of disorders, such as eczema, psoriasis, and acne.

→ Grice EA, et al. *Science* 2009;324(5931):1190-2. PMID: 19478181.
→ For more information, see http://nihroadmap.nih.gov/hmp/index.asp

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (I) (**NHGRI**, Common Fund - all ICs participate, NCI)

ENCODE: The ENCyclopedia Of DNA Elements (ENCODE) is an international research consortium organized by NIH that seeks to identify all functional elements in the human genome. Until now, most studies have concentrated on the 1 percent of the genome that contains protein-coding genes, overlooking the many other parts of the human genetic blueprint that are important to biological function. ENCODE's exciting discoveries may well reshape the way scientists think about the genome and pave the way for more effective approaches to understanding and improving human health. Efforts to uncover functional elements also extend to some of the organisms most often used in biomedical research. The model organism ENCyclopedia of DNA Elements (modENCODE) Project is analyzing the genomes of the fruit fly, *Drosophila melanogaster*; and the round worm, *Caenorhabditis elegans*. The data that are expected to result from modENCODE project will provide important insights into the biology of these model organisms, as well as provide a valuable tool for comparative studies aimed at understanding human biology.

→ For more information, see http://www.genome.gov/10005107
→ For more information, see http://www.genome.gov/26524507
→ (E) (**NHGRI**)

Genetics of Diabetes: Diabetes is a common, potentially deadly and debilitating chronic disease that poses an enormous health care burden. Both of the most common forms of diabetes, type 1 and type 2, are caused by an intersection of genetic and environmental risk factors. Although genetic effects on developing diabetes are profound, they are not simple, as there are many genes that influence the likelihood of developing type 1 or type 2 diabetes. Further, ethnicity impacts both genetic and environmental risk factors. To learn more about diabetes genetics, particularly through new genomic technologies, NIH supports the Type 1 Diabetes Genetics Consortium to study type 1 diabetes, and several major grants to study the genetics of type 2 diabetes. These programs now have identified at least 40 genetic regions linked to type 1 diabetes and at least 38 type 2 diabetes genes. Other studies are refining our understanding of how these genes affect diabetes risk. Many of these projects are geared to collect data from multiple ethnic groups, but a recent initiative sought to advance knowledge of diabetes risk genes in specific racial and ethnic groups disproportionately affected by type 2 diabetes, to understand how different genes affect different populations.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-004.html
→ For more information, see http://www.t1dgc.org
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIDDK**, NHGRI, NIAID, NICHD)

Advances in Understanding the Genomic Risk for Schizophrenia: Three genome-wide studies have pinpointed a vast array of genetic variation that cumulatively poses the greatest risk for schizophrenia yet reported. All three studies implicate an area of chromosome 6 (6p22.1), which is known to harbor genes involved in immunity and genes that control how and when genes turn on and off. Among sites showing the strongest associations with schizophrenia was a suspect area on chromosome 22 and more than 450 variations in the suspect area on chromosome 6. Individually, these variants' effects statistically were insignificant, but cumulatively they were very powerful. Additionally, one of the studies traced schizophrenia and bipolar disorder, in part, to the same chromosomal neighborhoods. These findings suggest that if some of the same genetic risks underlie schizophrenia and bipolar disorder, then these disorders may originate from a common vulnerability in brain development.

→ Shi J, et al. *Nature* 2009;460(7256):753-7. PMID: 19571809. PMCID: PMC2775422.
Stefansson H, et al. *Nature* 2009;460(7256):744-7. PMID: 19571808.
International Schizophrenia Consortium, et al. *Nature* 2009;460(7256):748-52. PMID: 19571811.
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIMH**)

The Collaborative Study on the Genetics of Alcoholism (COGA): In its 20th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) that are densely affected by alcoholism, enabling researchers to take a multigenerational perspective. A recent COGA study focusing on adolescents follows individuals longitudinally as they transition through the age of risk. Investigators have identified several genes, including *GABRA2, ADH4, ADH5, CHRM2, GRM8, GABRR1,* and *GABRR2* (*Rho 1* and *2*) that influence the risk for alcoholism and related behaviors, such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected, and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes that influence vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

→ Xuei X, et al. *Am J Med Genet B Neuropsychiatr Genet* 2009;150B(3):359-68. PMID: 19536785. PMCID: 2829340.
→ For more information, see http://zork.wustl.edu/niaaa
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIAAA**) (GPRA)

New Genetics/Epigenetic Tools Shed Light on Addiction: NIH-supported research is taking full advantage of expanding databases and fast technologies to identify links between genetic variations and disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms underlying complex diseases like addiction, which genes strongly influence. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as "gene chips" (e.g., the neurexin gene has been found to play a role in drug addiction). Applying these tools to addiction and other brain disorders advances our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient's genetic profile. To complement these efforts, NIH is investing in the equally important field of epigenetics, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the deleterious long-term changes to brain circuits from drug abuse. For example, using a powerful new technique known as ChIP-on-chip to monitor epigenetic changes correlated with gene activity, investigators recently have mapped the genomic effects of chronic cocaine use in the reward center of the mouse brain. Such analyses provide needed information about which genes are altered by cocaine and can point to new targets for medications development. Epigenetic discoveries also can inform ways to smartly alter environmental factors so as to decrease the risk for drug abuse and addiction.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-015.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-016.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-003.html

→ For more information, see http://nihroadmap.nih.gov/epigenomics/initiatives.asp
→ For more information, see http://nihroadmap.nih.gov/commonfundupdate.asp
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E/I) (**NIDA**, NCI, NIAAA, NIMH) (GPRA)

Regulation of Gene Expression by Chemically Marking DNA: Studies by NIH intramural scientists of how genes are turned on (expressed) or off have provided insight into gene regulation and the overall organization of the genome. For example, a recent study indicated the importance of a mammalian protein called Vezf1 in maintaining the integrity of the genome. This protein previously had been identified by research on an "insulator" element—a segment of DNA that marks boundaries in the genome and allows neighboring genes to be regulated independently. Research on insulator elements—found in fruit flies, chickens, and mammals—has provided great insight into the molecular mechanisms used by the cell to turn on certain genes while keeping other genes turned off. In studies of Vezf1, the scientists discovered that deletion of the gene encoding the Vezf1 protein in a mouse embryonic stem cell line led to loss of specific chemical marks on the DNA at widespread sites in the genome. This type of chemical mark, known as DNA methylation, is a signal used by the cell to turn a gene off. The scientists also demonstrated that the loss of DNA methylation observed when Vezf1 was deleted was due to a decrease in the amount of a specific protein that puts this mark on the DNA. Therefore, Vezf1 is required for the DNA methylation pattern in these cells. Continued studies of insulators and their associated proteins will lead to further understanding of the regulation of genes, an essential process for health and development.

→ Gowher H, et al. *Genes Dev* 2008;22(15):2075-84. PMID: 18676812. PMCID: PMC2492749.
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (I) (**NIDDK**)

Genetics of Chronic Kidney Disease: Researchers recently have made progress in uncovering the role of genetics in chronic kidney disease (CKD) arising from various causes. Scientists recently have identified a genetic region that is strongly associated with CKD in African Americans that arises as a consequence of conditions other than diabetes, such as high blood pressure and HIV-associated kidney disease. Several variants associated with the *MYH9* gene were identified as major contributors to excess risk of this kind of CKD among African Americans. This finding suggests that CKD may proceed along different paths depending on whether diabetes or another condition is the underlying disorder. The Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to study progression of an inherited form of kidney disease, polycystic kidney disease (PKD). Phase I of the study demonstrated that magnetic resonance imaging accurately could track structural changes in the kidneys; Phase II showed that patients with mutations in the *PKD1* gene have more cysts and larger kidneys than patients with *PKD2* mutations. A planned third phase of CRISP will provide critical information about the validity of changes in kidney volume as a surrogate marker for loss of kidney function. NIH also has launched a study to identify and validate biomarkers and risk assessment tools for kidney function, injury, and disease progression in patients with CKD, to predict risk, aid early diagnosis, and assess disease progression.

→ Kopp JB, et al. *Nat Genet* 2008;40(10):1175-84. PMID: 18794856.
Kao WHL, et al. *Nat Genet* 2008;40(10):1185-92. PMID: 18794854. PMCID: PMC2614692.
Grantham JJ, et al. *New Engl J Med* 2006;354(20):2122-30. PMID: 16707749.
Rule AD, et al. *J Am Soc Nephrol* 2006;17(3):854-62. PMID: 16452494.
→ For more information, see http://www.nih.gov/news/health/sep2008/niddk-14.htm
→ For more information, see http://www.nih.gov/news/pr/may2006/niddk-17.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
→ (E/I) (**NIDDK**, AHRQ, NCI, NCRR, NHLBI)

Genotyping Information for Use in Warfarin Therapy: The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), a component of the Pharmacogenetics Research Network (PGRN), sponsors data-sharing consortia. In 2009, one of the consortia, the International Warfarin Pharmacogenetics Consortium (IWPC), completed its first project: Clinical and genetic data from more than 4,000 patients worldwide who received warfarin were assembled into a large dataset to create a universal dose algorithm that incorporated genetic factors along with clinical factors. This established a better method to calculate the initial dose of the anticoagulant, and NIH will use the information for a prospective clinical trial to determine the value of pre-prescription genotyping. Further genomic analyses of the warfarin data set are underway. Based upon the success in this endeavor, more consortia were created in 2009. The International Tamoxifen Pharmacogenetics Consortium (ITPC) was formed to gather genetic and clinical data on the efficacy and toxicity of tamoxifen from patients around the world to test for specific associations between genetic variants and clinical effects, and the International Severe Irinotecan Neutropenia Consortium (INSINC) was formed to assemble a large dataset to answer questions definitively relating to genetic effects on adverse outcomes of irinotecan therapy, and to provide tools for evaluating toxicity risk.

→ International Warfarin Pharmacogenetics Consortium, et al. *N Engl J Med* 2009;360(8):753-64. PMID: 19228618. PMCID: PMC2722908.
→ For more information, see http://www.nigms.nih.gov/Initiatives/PGRN
→ For more information, see http://www.pharmgkb.org/views/loadConsortia.action
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NIGMS**, NCRR, NHLBI, NINDS) (GPRA)

Understanding the Progression from a Skin Disorder to Asthma in Children: NIH-funded researchers investigating basic biochemical mechanisms involved in development have discovered a mechanism that can explain how 50-70 percent of young children affected with the skin rashes of atopic dermatitis (a type of eczema) eventually become asthmatic. The process involves the overproduction of a specific signaling molecule by inflamed skin cells that can trigger the hypersensitivity characteristic of asthma in lung cells. This mechanism and possible ways to prevent this "atopic march" and the development of asthma in general are being actively evaluated in animal models as well as in early human studies.

→ For more information, see http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1000067
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIGMS**)

Genetic Epidemiology of COPD (COPDGene): This investigator-initiated research program is performing genetic testing in more than 10,000 current or former smokers to identify genes that are associated with the presence of COPD (chronic obstructive pulmonary disease). In this large and diverse cohort, half of the subjects will be women and one-third will be African American. Although COPD is the fourth most common cause of death in the United States, understanding why some smokers develop serious lung disease and others do not is lacking. Genetics studies may reveal factors that determine this differential susceptibility to disease. The COPDGene study will help to identify individuals at greatest risk, point to particular molecular pathways that may be involved in pathogenesis, and suggest possible targets for prevention and drug therapy. The phenotypic and genetic data generated by the program will be made available through an NIH data repository to allow additional research analyses by other investigators. COPDGene has thus far enrolled more than 4,000 subjects at 17 sites across the United States.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NHLBI**)

Challenge Program in Integrative Research: Mechanisms of Susceptibility to Oxidative-Stress Disease: This project is an interdisciplinary, collaborative effort to combine the use of simple eukaryotic systems, mouse models, genetic polymorphisms, genomics, clinical research, and patient samples to investigate the mechanisms of susceptibility to the development of oxidative stress-induced disease. The initial phase of the program is focused on bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP), chronic diseases associated with very low birth weight infants. This program consists of three interactive projects: (1) positional cloning of BPD/ROP susceptibility genes in inbred mice; (2) investigating the role of mitochondrial reactive oxygen species in hyperoxia-induced tissue injury; and (3) searching for oxidant susceptibility genes and neonatal diseases in prospective case-parent triad cohorts. Together this group will identify stress response networks, develop and validate early biomarkers of disease, and identify candidate genes and genetic polymorphisms that influence susceptibility to oxidative stress. This program has established a highly collaborative research team uniting bench science with clinical research and patient outcomes. The long-term goal of this program is to understand the role of specific genes that increase human susceptibility to oxidant stress-induced diseases. Thus, this team has the potential to affect a large number of environmentally induced diseases associated with inflammation and reactive oxygen species, including asthma, atherosclerosis, cancer, cardiovascular disorders, and neurodegenerative diseases.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (I) (**NIEHS**)

Longevity Assurance Gene (LAG) Initiative and Interactive Network: The NIH-supported LAG Initiative has been one of the most successful research initiatives in the field of aging biology and has generated a number of highly significant advances in our understanding of the biological pathways and mechanisms responsible for extension of life span and health span in model organisms. Notably, the LAG initiative has led to the identification of more than 100 new longevity-associated genes, along with many other conserved biological processes and pathways that regulate longevity in a host of divergent species, including humans. Several longevity genes and pathways identified in model organisms as part of the LAG Initiative now are being studied in human populations to determine if analogous genes/pathways are involved in determining human longevity and health span.

→ (E) (**NIA**)

Confronting the Challenge of Antimicrobial Resistance: Antimicrobial resistance has become a major public health threat that is severely jeopardizing the utility of many "first-line" antimicrobial agents. The development of resistance can be caused by many factors, including the inappropriate use of antibiotics. NIH supports a robust basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes. NIH also is pursuing translational and clinical research in this area, including clinical studies to test interventions for community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection and to evaluate the efficacy of off-patent antimicrobial agents. NIH laboratories are at the forefront of understanding the fundamental causes of resistance—from studies of the disease-causing organisms and the progression of disease to research on the advantages and shortcomings of current antibiotics. Specific research foci of NIH researchers and NIH-supported grantees include MRSA and vancomycin-resistant *Staphylococcus aureus* (VRSA) (commonly acquired in community settings), and drug-resistant malaria and tuberculosis. NIH supports genomic sequencing through its Microbial Sequencing Centers; researchers at these centers have sequenced the genomes of numerous disease-causing bacteria, viruses, parasites, and fungi, which may help identify mechanisms of resistance and when and where resistance emerges.

→ For more information, see http://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm

→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAID**) (GPRA)

The Multi-Ethnic Study of Atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter epidemiological study of cardiovascular disease (CVD) in 6,914 men and women from 4 ethnic groups—white, African-American, Hispanic, and Chinese—who have been followed for almost 10 years to identify predictors of progression of subclinical CVD. The study originally was funded from 1999 to 2008 and subsequently renewed through 2015. It has measured and compared the predictive value of chest computed tomography, cardiac magnetic resonance imaging, carotid ultrasound, arterial compliance, endothelial function, biochemical markers, and genetic and environmental factors for the development of CVD. MESA has major ongoing ancillary studies in the areas of air pollution (funded by the EPA), chronic lung disease, and genetics. MESA SHARe (SNP Health Association Resource) will combine genome-wide scans with detailed phenotypic information and share these data with the scientific community for genome-wide association analyses.

→ For more information, see http://mesa-nhlbi.org
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NHLBI**, NEI)

Revolution in Technology

Genome Technology and the $100,000 and $1,000 Genome Initiatives: Taking the discoveries made in genetic research initiatives and delivering them to patients on a much wider basis will require significant decreases in the cost and time needed to sequence an entire human genome. Rapid gains have been made on this front since the start of the Human Genome Project and costs continue to fall dramatically. However, it still remains prohibitively expensive to sequence the genomes of individual patients in the clinic. Developing technology to make genome sequencing more affordable is essential for making genomic information part of routine medical care. NIH's Genome Technology program supports research to develop rapid, low-cost methods, technologies, and instruments that will:

- Read DNA sequences
- Check sequences for genetic variations (SNP genotyping)
- Aid research to understand the effects of genetic variations on genomic function.

In 2004, NIH began funding research to develop technologies specifically intended to lower the cost of sequencing the amount of DNA in a human genome, about 3 billion base pairs. These efforts include:

- "Near-Term Development for Genome Sequencing" Grants. These awards support research to enable the sequencing of a human-sized genome for about $100,000.
- Revolutionary Genome Sequencing Technologies Grants. These awards aim to develop breakthrough technologies that will enable an individual's genome to be sequenced for $1,000 or less.

→ For more information, see http://www.genome.gov/10000368
→ For more information, see http://www.genome.gov/27527585
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NHGRI**)

NIH Roadmap Technology Development in Epigenetics: The key focus of the Technology Development in Epigenetics initiative is to foster the development of revolutionary technologies with the potential to significantly change how epigenomics research is performed in the future. Although the technologies and tools for evaluating epigenetic events are improving, existing constraints impede even more rapid progress. Nine grants were funded in 2009 as the result of this initiative. Five of the funded R01 scientists were new investigators. In the future, technological improvements in epigenome-wide mapping and related technologies may enable epigenomic changes to be used to diagnose and investigate the effects of environmental exposures (e.g., drugs of abuse, toxins, infection) on disease (e.g., cancer, neuropsychiatric disorders, aging).

→ For more information, see http://nihroadmap.nih.gov/epigenomics/
→ (E) (**NIDA**, Common Fund - all ICs participate)

DNA in 3-D: The sequence of the 3 billion DNA base pairs that make up the human genome holds the answers to many questions related to human development, health, and disease. Consequently, much research aimed at understanding the genome has focused on decoding the information conveyed by the linear order of DNA bases. Now, a team that includes an NIH intramural researcher has devised a new way of analyzing functional regions the human genome. The novel approach involves looking at the three-dimensional shape of the genome's DNA, rather than just the base pair sequence. By combining chemical and computer analyses, the researchers survey the landscape, or topography, of DNA structure for areas likely to play a key role in biological function. The method involves identifying all of the grooves, bumps, and turns of the DNA that makes up the human genome and then comparing those structural features to those seen in the genomes of other animal species. Structural features that have been preserved across many species are likely to play important roles in how the human body functions, while those that have changed a great deal over the course of evolution may play a less central role or no role at all.

→ Parker SC, et al. *Science* 2009324(5925):389-92. PMID: 19286520. PMCID: PMC2749491.
→ For more information, see http://www.genome.gov/27530624
→ (I) (**NHGRI**)

Scientists Accomplish Initial Catalogue of the Human Salivary Proteome: Secretions from the major salivary glands (parotid, submandibular, and sublingual) contain many peptides and proteins. They contribute to saliva's important roles in maintaining oral health, including antimicrobial, lubricating, buffering, and digestive properties. Salivary gland disorders, which result in severe dry mouth, compromise quality of life because they often lead to decay and periodontal diseases, mucosal infections, halitosis, taste impairment, and difficulties in swallowing and speaking. Saliva is a complex fluid; over the years, a number of salivary proteins have been reported but a systematic approach to catalogue all the proteins present in saliva was only initiated in 2004. NIH supported three teams of investigators to conduct the first comprehensive analysis of the salivary proteome. After samples were collected and analyzed, the data were standardized and integrated, yielding a salivary proteome that comprises 1,166 proteins. Of these proteins, 152 parotid and 139 submandibular/sublingual proteins were identified by all three research groups; these proteins form the core proteome. Most proteins identified were extracellular or secretory proteins, and involved in numerous molecular and cellular processes. A significant number of proteins represented in the salivary proteome also have been found to exist in the plasma or tear proteomes. This initial catalogue of the salivary proteome is a significant first step toward a comprehensive understanding of what the functions of saliva are, and how salivary composition is dependent on physiological variations, including on health and disease. This proteome could be the source of potential diagnostic and prognostic biomarkers for oral and systemic conditions.

→ Denny P, et al. *J Proteome Res* 2008;7:1994-2006. PMID: 18361515.

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NIDCR**)

Increased Efficiency for Genetic Engineering Research Methods: Gene therapy—the ability to cure a genetic disease by replacing or destroying the faulty copy of a gene—has been limited by the difficulty of designing chemical "bullets" that will zap the defective gene without affecting any of the other genes in a person's cells. Recently, NIH-supported researchers have developed a method, called OPEN, for creating gene-specific chemical bullets that is much faster, easier, and cheaper than alternative technologies. OPEN has the potential to revolutionize genetic engineering, and it will also greatly enhance the progress of genetic research in all organisms.

→ Maeder M, et al. *Mol Cell* 2008;31(2):294-301. PMID: 18657511. PMCID: PMC2535758.
→ (E) (**NIGMS**)

The Big Picture: Genome-Wide Association Studies

Genome-Wide Association Studies: With unprecedented speed, researchers have used an approach called genome-wide association studies (GWAS) to explore genetic variants and their complex relationships to human health and disease. GWAS research has linked a stunning number of genetic variants to common conditions—more than 130 in 2008 alone. For example, the obesity epidemic and its related health conditions pose a great challenge for the Nation. In 2008, the Genetic Investigation of Anthropometric Traits consortium identified six genes associated with body mass index, a key indicator for obesity. Also in 2008, three GWAS of lung cancer implicated several genes already known to be linked to nicotine addiction. In a feat that would not have been possible without the power of whole genome analysis, the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium in 2009 gathered data from participants in long-running studies to reveal genetic variants associated with an increased risk of stroke. Identification of genetic variants associated with common diseases opens new windows into the biology of health and disease. This work also raises the possibility of someday using genetic testing, in combination with family history, to identify at-risk, pre-symptomatic individuals who might benefit from personalized screening and preventive therapies.

→ For more information, see http://www.genome.gov/27528559
→ For more information, see http://www.genome.gov/27529231
→ For more information, see http://www.genome.gov/27531390
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E, I) (**NHGRI, NIDDK, NCI, NIA, NHLBI, NIMH**, NINDS)

Population Genomics, GAIN, and GEI: In 2006, HHS announced the creation of two groundbreaking initiatives for population genomics research in which NIH played a leading role. The Genetic Association Information Network (GAIN) was a public-private partnership involving NIH, the Foundation for NIH, Pfizer, Affymetrix, Perlegen, the Broad Institute, and Abbott. GAIN supported a series of genome-wide association studies designed to identify specific points of DNA variation associated with the occurrence of common diseases. Investigators from existing clinical studies were invited to submit samples and data on roughly 2,000 participants for genomic assays designed to capture roughly 80 percent of the common changes in the human genome. GAIN successfully concluded in November 2008, with the third and final public workshop on the project. At this meeting, investigators from across the research community shared their findings and discussed how they had used the data generated through GAIN in their own research. Data from the GAIN studies have been deposited into the NIH database of Genotype and Phenotype (dbGaP) for the broad use of the research community. Access is controlled by the GAIN Data Access Committee. Additionally, NIH funds the Genes, Environment, and Health Initiative (GEI), an NIH-wide effort combining comprehensive genetic analysis and environmental technology

development to understand the causes of common diseases. GEI has held a number of workshops to identify novel ways of analyzing the wealth of information gathered and to use that data to improve human health.

→ For more information, see http://www.genome.gov/19518664
→ For more information, see http://www.genome.gov/19518663
→ For more information, see http://genesandenvironment.nih.gov
→ For more information, see http://www.genome.gov/11511175
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E, I) (**NHGRI**, NIEHS, NLM)

Genome-Wide Association Studies of Autoimmune Disease Risk: In recent years, genome-wide association studies (GWAS) have transformed the identification of gene regions related to disease risk, through an unbiased analysis of patients with a disease, in comparison with people who don't have it. These GWAS require large numbers of patients and individuals without the disease to obtain statistically significant results. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects, in addition to productive, multisite collaborations across the United States, including international researchers and contributions from the NIH Intramural Research Program. GWAS have yielded important information about disease risk, as well as understanding of disease pathways and potential therapeutic targets, in several autoimmune diseases in the past 2 years. Diseases studied include psoriasis, rheumatoid arthritis, systemic lupus erythematosus (or lupus), ankylosing spondylitis, and type 1 diabetes. Initial results from GWAS require confirmation by replication in additional groups of patients. More detailed localization of disease risk genes can be achieved through comprehensive DNA sequencing of candidate gene regions. New NIH initiatives are supporting these follow-up studies, which are critical to validating GWAS findings.

→ Plenge RM, et al. *Nat Genet* 2007;39(12):1477-82. PMID: 17982456. PMCID: PMC2652744.
Wellcome Trust Case Control Consortium, et al. *Nat Genet* 2007;39(11):1329-37. PMID: 17952073. PMCID: PMC2680141.
Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
Liu Y, et al. *PLoS Genet* 2008;4(3):e1000041. PMID: 18369459. PMCID: PMC2274885.
Nair RP, et al. *Nat Genet* 2009;41(2):199-204. PMID: 19169254. PMCID: PMC2745122.
Barrett JC, et al. *Nat Genet* 2009;41:703-707. PMID: 19430480. PMCID: PMC2889014.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/10_04.asp
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-09-135.html
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2008/Ankyl_Spond_gene.asp
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-123.html
→ For more information, see http://www.nature.com/ng/journal/v41/n6/abs/ng.381.html
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NIAMS**, NCRR, NHGRI, NHLBI, NIAID, NICHD, NIDA, NIDCR, NIDDK)

Lupus: There have been significant advances in identifying disease risk genes for systemic lupus erythematosus (lupus) in recent years. Genome-wide association, linkage analysis, and direct sequencing have revealed genetic variations in lupus patients for molecules involved in immune mechanisms and regulation, inflammation, and vascular cell activities. The disease affects women disproportionately, with female lupus patients outnumbering males nine to one. African American women are three times as likely to get lupus as Caucasian women, and it also is common more in Hispanic, Asian, and American Indian women. These results are being replicated in distinct racial and ethnic populations. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects. Another critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by

government agencies, private foundations, and industry. The numerous genes uncovered in these studies reflect the complex expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene specifically is associated with severe forms of lupus that include kidney disease, but not skin manifestations. Methods to analyze patients' blood samples are being developed to group disease-specific variations in gene expression according to pathogenic mechanisms. This system may be used to predict flares of lupus activity in the future and guide individualized treatment. Lupus risk genes also have been discovered on the X chromosome and reproduced in animal models of the disease. These important findings shed light on the female predominance of lupus.

→ Edberg JC, et al. *Hum Mol Genet* 2008 Apr 15;17(8):1147-55. PMID: 18182444.
Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), et al. *Nat Genet* 2008;40(2):204-10. PMID: 18204446.
Taylor KE, et al. *PLoS Genet* 2008;4(5):e1000084. PMID: 18516230. PMCID: PMC2377340.
Chaussabel D, et al. *Immunity* 2008;29(1):150-64. PMID: 18631455. PMCID: PMC2727981.
Smith-Bouvier DL, et al. *J Exp Med* 2008;205(5):1099-108. PMID: 18443225. PMCID: PMC2373842.
Scofield RH, et al. *Arthritis Rheum* 2008;58(8):2511-7. PMID: 18668569.
Jacob CO, et al. *Proc Natl Acad Sci U S A* 2009;106(15):6256-61. PMID: 19329491. PMCID: PMC2669395.
→ This example also appears in Chapter 2: *Autoimmune Diseases*, Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAMS**, NCI, NCRR, NHLBI, NIAID, NIDCR, NINDS)

Psoriasis: Early studies of families of psoriasis patients indicated a genetic susceptibility for the disease. Genome-wide association studies (GWAS) have revealed genetic variations in psoriasis patients for previously identified immune system proteins. New disease risk genes, which are associated with inflammation and immune function, also have been found. Some of these variations occur in or near gene regions associated with other autoimmune diseases, such as rheumatoid arthritis, lupus, and Crohn's disease, although in distinctly independent genes. In addition to variations in genes associated with immune function, GWAS have uncovered differences among psoriasis patients in genes involved with skin differentiation and regulation of inflammation.

→ Liu Y, et al. *PLoS Genet* 2008;4(3):e1000041. PMID: 18369459. PMCID: PMC2274885.
Nair RP, et al. *Nat Genet* 2009;41(2):199-204. PMID: 19169254. PMCID: PMC2745122.
→ This example also appears in Chapter 2: *Autoimmune Diseases*
→ (E) (**NIAMS**, NIDA)

Seeking Solutions for People with Sjogren's Syndrome: Sjogren's syndrome is one of the most prevalent autoimmune disorders, affecting as many as 4 million people in the United States. Nine out of 10 patients affected are female. It is an autoimmune disease that progressively destroys salivary and lachrymal glands. The most common symptoms include dry eyes, dry mouth, fatigue, and musculoskeletal pain. A significant roadblock for moving discoveries ahead in the field of Sjogren's syndrome is the lack of data and biospecimens available for research. Recognizing the problem, NIH spearheaded an effort to establish Sjogren's patient registries at two extramural institutions as well as through its own intramural program. These groups are working together to generate and share with the general research community the genome-wide genotyping data and clinical information from the cohorts enrolled through these efforts. This resource should jumpstart efforts to understand genetic contributions to Sjogren's syndrome and the etiologic overlap with related autoimmune conditions such as lupus and rheumatoid arthritis. In addition to participating in the patient registry and genotyping efforts described above, the Sjogren's Syndrome Clinic, located in the NIH CC, collects systematic clinical and laboratory data on the Sjogren's syndrome (and salivary dysfunction) population. Gene therapy and bioengineering hold promise for the repair or even replacement of salivary glands ravaged by Sjogren's syndrome. More than 300 patient visits

occur annually, and the clinic is expanding its patient recruitment to accelerate the conduct of clinical trials that might shed light on this disorder.

→ Korman BD, et al. *Genes Immun* 2008;9(3):267-70. PMID: 18273036.
Roescher N, et al. *Oral Dis* 2009;15(8):519-26. PMID: 19519622. PMCID: PMC2762015.
Nikolov NP, Illei GG. *Curr Opin Rheumatol* 2009;21(5):465-70. PMID: 19568172. PMCID: PMC2766246.
→ For more information, see http://www.sjogrens.org/
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NIDCR**, CC, ORWH)

SNP-Health Association Resource (SHARe): SHARe conducts genome-wide association studies in several large NIH cohort studies to identify genes underlying cardiovascular and lung diseases and other disorders such as obesity and diabetes. The resulting genotype data along with the cohort phenotype data are made available to researchers around the world through the NIH dbGAP database. Framingham SHARe, with 9,000 participants, was the first cohort released in this initiative due to its uniqueness in including 3 generations of participants with comparable data obtained from each generation at the same age. As of October 31, 2009, 95 projects to use these data had been approved. A modified version of the dataset was distributed to 72 approved research projects as the focus of a Southwest Foundation Genetic Analysis Workshop. The second cohort released was the SHARe Asthma Resource Project, which includes genotype data from more than 2,500 adults and children who have participated in NIH clinical research trials on asthma. As of October 31, 2009, 11 projects to use these data had been approved. Data from more than 12,000 African-American and Hispanic women from the Women's Health Initiative and approximately 8,300 participants from the Multi-Ethnic Study of Atherosclerosis were released in January 2010.

→ For more information, see http://www.nih.gov/news/pr/oct2007/nhlbi-01.htm
→ For more information, see http://nih.gov/news/health/dec2008/nhlbi-15.htm
→ For more information, see http://view.ncbi.nlm.nih.gov/dbgap/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NHLBI**, NLM)

Unraveling the Complexity of the Genetics of Glaucoma: Glaucoma is a group of eye disorders that share a distinct type of optic nerve damage, which can lead to blindness. It is the leading cause of blindness in African Americans. More than 2 million Americans have been diagnosed with glaucoma, and the prevalence of the disease will rise to a projected 3 million by 2020. Glaucoma research aims to understand the complex genetic factors that lead to common forms of the disease and to develop treatments that protect ganglion cells of the retina from the damage that leads to vision loss. Under GPRA, NIH set a goal by 2012 to identify the genes that control the risk of glaucoma. To achieve this goal, NIH launched a large genome-wide association study to identify glaucoma risk genes. NEIGHBOR (NEI Glaucoma Human Genetics CollaBORation) is a unique collaborative effort involving 22 investigators at 12 institutions throughout the United States. Approximately 2,000 cases and 2,000 age, sex, and ethnically matched controls will have their complete genome sequenced (genotyped) for a genome-wide association study to identify genetic variants associated with the disease. Genetic data and associated disease characteristics collected from NEIGHBOR will be made available to the research community through the NIH database of Genotypes and Phenotypes (dbGaP).

→ Friedman DS, et al. *Arch Ophthalmol* 2004;122(4):532-8. PMID: 15078671.
→ For more information, see http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/about.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NEI, NLM**) (GPRA)

Decoding Cancer

Genomic Research on Tumor Cells: In addition to supporting The Cancer Genome Atlas with NCI, NHGRI operates a number of other cancer-focused research programs, both intramural and extramural. The Tumor Sequencing Project (TSP) is a multicenter effort to characterize the genomic changes that occur in lung adenocarcinoma, the most common type of lung cancer in the United States. In 2008, TSP researchers identified 26 genes that often are mutated in these lung tumors, more than doubling the list previously known to scientists and clinicians. In other efforts, a team of NHGRI intramural and NHGRI-funded researchers recently identified an inherited gene alteration linked to increased susceptibility to lung cancer. With further investigation, the researchers said it may be possible to use this genetic information to identify high-risk people who could benefit from earlier, more aggressive screening for lung cancer, in much the same way as women who inherit *BRCA1* and *BRCA2* breast cancer genes may benefit from early mammography and other tests. Other NHGRI work has focused on the most deadly type of skin cancer, melanoma. In 2009, an NHGRI intramural researcher discovered a gene that acts as a tumor suppressor in melanoma. This finding is significant because researchers previously thought drugs that blocked that gene or its protein might offer a new way to treat melanoma, when, in fact, a better strategy might be to activate the gene.

→ For more information, see http://genome.gov/27528559
→ For more information, see http://healthnews.uc.edu/news/?/8427/
→ For more information, see http://genome.gov/27530882
→ (E, I) (**NHGRI**, NCI)

Genome-Wide Association Studies of Cancer Risk: The Cancer Genetic Markers of Susceptibility (CGEMS) project is a signature initiative that uses genome-wide association studies (GWAS) to identify genetic variants and mechanisms associated with cancer risk. Understanding these variants and mechanisms may lead to new preventive, diagnostic, and therapeutic interventions. CGEMS investigators have pinpointed genetic variants associated with elevated prostate cancer risk as well as variants associated with increased breast cancer risk. The same genetic variant was shown to be involved in increased prostate, colon, and other cancers, suggesting a common mechanistic pathway for susceptibility to a variety of cancers. Another GWAS project, the Cohort Consortium, is a unique extramural/intramural collaboration that allows Consortium partners to share access to data on 37 cohorts comprised of 4 million people from diverse populations. Each cohort contains extensive information on known or suspected risk factors and biospecimens collected pre- and post-diagnosis. The large number of study subjects permits the detection of modest genetic effects, as well as studies of variants involved in less common cancers. One cohort within the Consortium, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cohort, includes about 2.9 million specimens. These pre-diagnostic specimens provide a valuable resource for studies of cancer etiology and early detection. Researchers can correlate changes in molecular profiles associated with the onset of different types of disease, thereby providing valuable insights into the actual mechanisms of human carcinogenesis.

→ For more information, see http://cgems.cancer.gov
→ For more information, see http://epi.grants.cancer.gov/Consortia/cohort.html
→ For more information, see http://www.parplco.org
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E/I) (**NCI**)

Research Tools for Genomic Studies of Cancer: The Cancer Genome Atlas (TCGA) is developing a publicly accessible, comprehensive catalog of the many genetic changes that occur in cancers. Tumor and matched normal samples are analyzed for genetic changes such as chromosome rearrangements and gene mutations; gene expression changes, including changes in expression patterns of microRNAs, as well as epigentic modifications (differences in the chemical modifications of DNA that influence gene expression). All data, including pre-publication data, are freely available through the TCGA website and are compatible with the cancer Bioinformatics Grid (caBIG®). The first TCGA project,

which focused on brain cancer (glioblastoma multiforme), demonstrated the feasibility and impact of large-scale NIH-coordinated cancer genome analysis. Comprehensive characterization of ovarian cancer with other tumor types will follow. The goal of the Cancer Genome Anatomy Project (CGAP) is to provide cancer researchers with tools, resources, and information derived from studies that are characterizing differences between cancer and normal cells. The CGAP website provides access to data, bioinformatic tools, and information about available full-length cDNAs and short hairpin RNA clones. These resources are helping scientists conduct the research necessary to improve detection, diagnosis, and treatment of cancer. In the past year, new projects that explore molecular characterization through novel technologies were added as part of the Cancer Genomic Technology Initiative (CGTI). REMBRANDT is the national portal for molecular, genetic, and clinical data associated with several thousand primary brain tumors. This framework provides researchers the ability to answer basic questions related to a patient or patient populations and view integrated datasets in a variety of contexts.

→ For more information, see http://cancergenome.nih.gov/index.asp
→ For more information, see http://cgap.nci.nih.gov/
→ For more information, see https://caintegrator.nci.nih.gov/rembrandt/
→ For more information, see http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm
→ This example also appears in Chapter 2: *Cancer*
→ (E/I) (**NCI, NHGRI**, NINDS) (ARRA)

Ethical, Legal, Social and Behavioral Issues

NIH Revision Awards for Studying Interactions Among Social, Behavioral, and Genetic Factors in Health: NIH issued three program announcements with review (PARs) to support competitive supplements for NIH grantees to study how interactions among genetic and behavioral/social factors influence health and disease. NIH is committing $7.9 million to support 11 applications submitted in response to these announcements, which will enable the addition of a genetics/genomics component to ongoing behavioral or social science research projects. The knowledge gained by such research will improve our understanding of the determinants of disease as well as inform efforts to reduce health risks and provide treatment.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/par-08-065.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-066.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-067.html
→ For more information, see http://obssr.od.nih.gov/scientific_areas/Genes_Beh_Environ/index.aspx
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**OBSSR**, NCCAM, NCI, NEI, NHGRI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIMH, NINDS, NINR, ODP/ODS)

Nonhuman Genomes

Microbial Genomics: NIH has made significant investments in large-scale, whole-genome sequencing of pathogens over the last decade. NIH also provides comprehensive genomic, bioinformatic, and proteomic resources and reagents to the scientific community:

- The NIH Genome Sequencing Centers of Infectious Diseases rapidly produce high-quality genome sequences of human pathogens and invertebrate vectors of diseases. Over the last decade, NIH has supported large-scale, whole-genome sequencing of pathogens and vectors. Thousands of bacteria, fungi, parasites, invertebrate vectors of diseases, and viruses have been sequenced, including pathogens that cause anthrax, influenza, aspergillosis, TB, gonorrhea, chlamydia, and cholera. For example, more than 3,733 human and avian influenza isolates have been sequenced including almost 500 for H1N1 (as of December 2009).

- The Pathogen Functional Genomics Resource Center generates and distributes genomic data sets, reagents, resources, bioinformatic analysis tools, and technologies for functional analysis of pathogens and vectors.
- Clinical Proteomics Centers for Infectious Diseases and Biodefense apply state-of-the art proteomics technologies for the discovery, quantification, and verification of protein biomarkers in infectious diseases. These data are released to the scientific community and may aid in the production of vaccines, diagnostics, and therapeutics.
- Systems Biology Centers for Infectious Diseases bring together a diverse group of scientists to analyze, identify, quantify, model, and predict the overall dynamics of microbial organisms' molecular networks and their host interactions using both computational and experimental methodologies.

→ For more information, see http://www3.niaid.nih.gov/topics/pathogenGenomics/default.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E/I) (**NIAID**)

Comparative Genomics: One of the primary objectives of today's biomedical research is to define and understand how the human genome functions, how malfunction leads to disease, and how that knowledge can be used to develop new preventive strategies, diagnostic methods, and therapies. Comparison of the genome sequence of humans with those of other organisms identifies regions of similarity and difference, providing insight into the evolution, structure, and function of human genes and pointing to new pathways to combat human disease. Currently, the genome sequences of 197organisms are either in the pipeline or have been completed through NHGRI funding. Ongoing sequencing targets include mammals, fungi, multiple strains of yeast, and additional nonhuman primates. NHGRI funds this work by supporting three large-scale sequencing centers that are world-renowned for their cost-effective, high-quality work. Recent highlights of this sequencing program include the publication of the genome of domestic cattle, the first livestock mammal to have its genetic blueprint sequenced and analyzed.

→ Bovine Genome Sequencing and Analysis Consortium, et al. Science 2009;324(5926):522-8. PMID: 19390049.
→ For more information, see http://www.genome.gov/10001691
→ (E) (NHGRI)

Resources

NIMH Center for Collaborative Genetic Studies: Over the last decade, NIH has built the infrastructure for large-scale genetic studies by creating the NIMH Center for Collaborative Genetic Studies (CCGC), a repository of DNA, cell cultures, and clinical data that serves as a national resource for researchers studying the genetics of complex mental disorders. In FY 2008, NIH launched a number of initiatives to enrich the repository through the collection of new biomaterials and clinical data from large cohorts. The CCGC will be enhanced through the creation of a genomic cyberinfrastructure that will integrate and manage data to accelerate genetic analyses. NIH also issued a RFA to encourage studies that will tease apart the complex genetic components of mental disorders, using resources within the CCGC. Projects will study the relationship between genes and illness-specific characteristics, interactions between multiple vulnerability genes, and the role of environmental and experiential influences on gene expression. Through these collective efforts, this research may give us the tools to predict vulnerability, validate diagnosis, and identify targets for new, effective, and personalized mental health treatments.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-130.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-131.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-120.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-121.html
→ For more information, see http://nimhgenetics.org/
→ (E) (**NIMH**)

Genetic and Genomic Resources for Emerging Non-Mammalian Model Organisms: In FYs 2008 and 2009, NIH funded 13 grants that create genetic and genomic resources for model organisms whose genomes recently have been sequenced. These organisms include fish, invertebrates, and microbes used to understand human health, development, and disease. The resources include reagents and mutant lines, a center for high-throughput mutagenesis, genetic maps, databases, and stock centers.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-457.html
→ (E) (**NIGMS**)

Reference Epigenome Mapping Centers: The Reference Epigenome Mapping Centers (REMCs), one of the Roadmap Epigenomics initiatives, are developing resources in reference epigenomes that the field has been requesting for the last 5 years, as indicated by recommendations made at several workshops and conferences focused on epigenetics and human health and disease. The funded centers form a network collaborating to provide comprehensive maps of all known epigenetic marks across a set of mutually agreed-upon reference cell types. This consortium, with input from advisors, will identify the most appropriate cell populations and determine standardized methods for growing or acquiring the cells so that data can be compared and integrated maps can be generated. The network of REMCs will produce comprehensive, high resolution, experimental data on epigenetic marks in specific cell populations, such as high-quality, pluripotent human embryonic stem cells, other human differentiating stem cells, and differentiated cell types including human cell types relevant to complex diseases of high public health significance. In addition, it will provide an informatics pipeline to generate high-quality reference epigenome maps from the centers' data; facilitate additional data analyses, in collaboration with the Epigenome Data Analysis and Coordinating Center, to integrate data from maps generated by REMCs from a specific cell type for different epigenetic marks; and conduct ancillary studies to develop limited data on functional aspects of epigenetic control of gene activity.

→ For more information, see http://nihroadmap.nih.gov/epigenomics/
→ For more information, see http://cancerres.aacrjournals.org/cgi/reprint/65/24/11241
→ For more information, see http://www.landesbioscience.com/journals/epigenetics/article/heindelEPI1-1.pdf
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIEHS, NIDA**, Common Fund - all ICs participate)

Discovery of Novel Epigenetic Marks in Mammalian Cells: The NIH Roadmap Epigenomics Program aims to accelerate the promise of epigenetics into applications that affect human health and a wide range of common complex human diseases by fostering the development of novel resources for research in this field. Epigenetics refers to various modifications to DNA, its associated proteins, or overall chromosome structure that influence whether genes are active or silent, independent of the DNA sequence. Research supported by this program will characterize the "epigenome," a catalog of the stable epigenetic modifications or "marks" that occur in the genome (and which may differ in different types of cells) and its impact on health and disease. One component of the program is an initiative to support research to identify novel epigenetic marks in mammalian cells and assess their role in the regulation of gene activity. It is anticipated that the results of these studies will be translated quickly to global epigenome mapping in human cells (conducted by the Epigenomics Roadmap Program's Reference Epigenome Mapping Centers). The eight research grants funded by this component of the program are expected to yield results that could have a significant impact on our understanding of gene regulation in mammals. In the long term, advances in these areas will enhance our ability to investigate, diagnose, and ameliorate human disease with a significant epigenetic component. For instance, NIH plans to build on these studies to examine the role of epigenomics in diabetes complications and to study effects of the intrauterine environment on the development of diabetes. Other research will examine epigenetic markers of beta cell differentiation.

→ For more information, see http://nihroadmap.nih.gov/epigenomics/initiatives.asp
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDDK**, Common Fund - all ICs participate)

Rodent Model Resources for Translational Research: Mouse and rat models are the primary testbed for preclinical research and have played a vital role in most medical advances in the last century. Rodent models comprise about 90 percent of all animal studies, enabling a wide range of genetic and physiological research on human disease. NIH plays a major role in supporting the availability of normal and mutant mice and rats for translational research. Recent accomplishments include:

- *Knockout Mouse Project (KOMP)*—A trans-NIH initiative to individually inactivate approximately 8,500 protein-coding mouse genes to better understand their genetic functions, which are, in many cases, very similar to human genes. High throughput production started in 2006, and international distribution of validated embryonic stem cell lines with specific knockouts from the KOMP Repository became fully operational in 2008. The KOMP is supported by 19 ICs and Offices.
- *Mutant Mouse Regional Resource Centers*—More than 1,700 mutant mouse lines, and 27,000 mutant embryonic cell lines, are available from the consortium, which comprises three centers across the United States.
- *Rat Resource and Research Center*—Acquisition and distribution of rat models increased dramatically in FY 2008, because of adaptation of novel technologies to make directed mutations.

→ For more information, see http://www.genome.gov/17515708
→ For more information, see http://komp.org
→ For more information, see http://www.nih.gov/science/models/mouse/knockout/komp.html
→ For more information, see http://www.mmrrc.org/
→ For more information, see http://www.nrrrc.missouri.edu
→ For more information, see http://www.ncrr.nih.gov/comparative_medicine/resource_directory/rodents.asp
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**, NHGRI, NIDA, NINDS)

Database of Genotype and Phenotype (dbGaP): Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics, and other scientific data, NIH established dbGAP to house the results of genome-wide association studies (GWAS), which examine genetic data of de-identified subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2009, dbGaP included results from more than 40 GWAS, including genetic analyses related to such diseases as Parkinson's disease, ALS, diabetes, alcoholism, lung cancer, and Alzheimer's disease. dbGaP is the central repository for many NIH-funded GWAS to provide for rapid and widespread distribution of such data to researchers and accelerate the understanding of how genes affect the susceptibility to and severity of disease.

→ For more information, see http://view.ncbi.nlm.nih.gov/dbgap
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**NLM**)

Ethical, Legal, and Social Implications (ELSI) Centers of Excellence: NHGRI's ELSI program has established a network of Centers of Excellence in ELSI Research. Currently, four full Centers and three exploratory Centers are bringing together investigators of diverse expertise to investigate issues related to:

- Intellectual property of genetic information
- Translation of genetic information to health care
- Genetic research that involves human participants
- Use of genetic information and technologies in non-health care settings, such as employment, insurance, education, criminal justice, or civil litigation
- Impact of genomics on the concepts of race, ethnicity, and individual and/or group identity
- Implications of uncovering genomic contributions to human traits and behaviors, such as aging or addictions
- How different individuals, cultures, and religious traditions view the ethical boundaries for the uses of genomics

→ For more information, see http://www.genome.gov/10001618
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NHGRI**)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects adipose tissue and alters hormonal control of sexual maturation. Endocrine distruptors, irradiation, and psychosocial elements also will be studied for effects.

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Molecular Biology and Basic Research

Who would have predicted that curiosity about a naturally glowing protein in the luminescent jellyfish Aequorea victoria would lead to the development of a tool that has transformed molecular and cellular biology? The 2008 Nobel Prize in Chemistry was awarded to Drs. Osamu Shimomura, Martin Chalfie, and Roger Tsien for the discovery and development of the green fluorescent protein (GFP).When attached to cellular molecules, GFP allows scientists to peer into living cells and observe molecular processes and cellular development. As is often the case with basic research studies, the yield on the initial research investment was not fully realized for many years. Dr. Shimomura first isolated GFP in 1962, yet it was not until more than 30 years later that Dr. Chalfie demonstrated that GFP could be used as a tag to observe biological processes in the bacteria E. coli and the simple roundworm C. elegans. Dr. Tsien, who studied the chemical basis of green fluorescence, has created a colorful palette of fluorescent proteins that have been used in exquisitely detailed cell biology studies. With GFP-based studies continuing to generate advances in biomedical research, the discovery and development of GFP have made a significant contribution to our understanding of fundamental biological processes underlying health and disease.

Introduction

Basic research is a major force driving progress across the biomedical and behavioral sciences and is paramount in uncovering the fundamental principles of biology, wellness, disease, and public health. Investments in basic biomedical and behavioral research make it possible to understand the causes of disease onset and progression, design preventive interventions, develop better diagnostic tests, and discover new treatments and cures. From the incremental advances in our understanding of a given disease to the groundbreaking discoveries that revolutionize our approaches for treating or preventing it, investments in basic research have and will continue to yield inestimable rewards and benefits to public health. As such, fostering a broad basic research portfolio is a critical component of fulfilling the NIH mission.

Uncovering Fundamental Aspects of Biology and Behavior through Basic Research

Biological function occurs over a huge span of spatial dimensions that ranges from organisms to cells to molecules. Despite the range in size, from meters to one-billionth of a meter—which is like comparing the diameter of the earth to the diameter of a marble—similar principles of structure, interaction, and dynamics govern biological function at the molecular, cellular, and organismal levels. These principles have been finely tuned to allow biological processes to play out in concerted harmony; however, disharmony can occur in molecular and cellular structures, interactions, and dynamics that often form the underlying basis of disease.

As examples of fundamental aspects of biology at the molecular level, scientists are interested in understanding how biological macromolecules—proteins, nucleic acids, sugars, and lipids—carry out cellular processes. What molecules are involved and what are their functions? How do their shapes define their functions? How do particular molecules interact to turn their functions on and off? And, how are innumerable molecular events properly coordinated to turn genes on and off, initiate cell growth and division, determine cell type, metabolize nutrients, and, when necessary, instruct a cell to die? Understanding how these events occur in wellness provides a framework for pinpointing molecular causes of disease.

At the cellular level, similar molecular questions are focused on understanding how cells sense and respond to their environment. How do cells interact and communicate with each other to form tissues and the organ structures of our body? How do cells process and distribute nutrients to disparate parts of the body? How do cells orchestrate a response to protect our body from invasion by foreign molecules? What is the molecular program that develops an initial ball of unspecialized cells into a fully functioning human being?

Similar to basic molecular and cellular biomedical research, basic behavioral research does not focus specifically on disease outcomes per se. Rather, it is designed primarily to elucidate knowledge about underlying mechanisms and

processes, knowledge that is fundamental to improving the understanding, explanation, observation, prediction, prevention, and management of illnesses, as well as the promotion of optimal health and well-being. Basic behavioral and social sciences research involves both human and animal studies, as well as many non-animal model systems, and spans the full range of scientific inquiry, from processes involved in the behavior of individuals, as individuals, to those involved in the interactions between and among individuals that explain inter-individual, group, organizational, community, population, macroeconomic, and other systems-level patterns of collective behavior. The domains and units of analysis can include intra-organismic as well as inter-organismic factors ("cells to society"), over varying units of time from nanoseconds to centuries, and lifespan developmental phases and phenomena that may occur within and across generations.

Basic Research Questions are Addressed through an Interdisciplinary Approach

The breadth of basic research questions spans all aspects of human development, physiology, behavior, and disease. Thus, basic research is encompassed in the missions of all NIH ICs. Progress in the basic sciences often requires interdisciplinary approaches. Expertise from multiple disciplines often is needed to develop new technologies, improve methods of data analysis, and provide insight on a fundamental disease pathway. NIH fosters collaborations that span all of the traditional and emerging disciplines of the life, physical, engineering, computer, behavioral, and social sciences.

The breadth of basic research questions spans all aspects of human development, physiology, behavior, and disease. Thus, basic research is encompassed in the missions of all NIH Institutes and Centers.

Although basic research is concerned with advancing our understanding of human health and disease, there are a number of reasons—both ethical and practical—that make humans poor subjects for exploring the fundamental aspects of biology. Therefore, scientists often carry out their basic research investigations in "model systems" that are simpler to work with in a precisely defined and controlled setting.

In the simplest experimental setting, researchers often remove the context of the organism and cell altogether and study individual molecules. By isolating a single type of protein, for instance, scientists can study its physical properties, functional activity, and three-dimensional structure. Understanding the structure and function of a protein allows researchers to design molecules that can selectively turn it "off" or "on" and forms the basis for the development of many pharmaceutical agents. In addition, these types of studies allow researchers to uncover how particular mutations alter molecular structure and function to cause disease.

An understanding of how molecules behave in isolation, however, must always be connected back to how they behave in a cellular setting. Scientists can study the function and interaction of molecules in cells grown in culture dishes in the laboratory. With the power of modern molecular biology, scientists can introduce virtually any gene of interest into a cell line to understand how it affects cellular outcomes, visualize how it interacts with different cellular components, and query how cellular processes are affected by particular disease-causing mutations. In addition to studying individual molecules in a cellular setting, researchers are more recently turning to "-omics" technologies to generate a systemwide picture of all of the molecules in a cell. This includes determining the sequences of all the genes in a certain cellular context (genomics), generating a profile of all the genes that are turned on or off in response to particular stimuli (transcriptomics), mapping out all of the protein-protein interactions and how they are modulated in different disease states (proteomics), following the path of all compounds generated by metabolism (metabolomics), and decoding the chemical markers that regulate gene expression (epigenomics). By amassing enormous data sets of gene sequences, protein-protein interactions, and gene expression profiles, systems biology researchers work to develop computational models to describe how all of these molecular components are integrated in normal health and disease.

With the power of modern molecular biology, scientists can introduce virtually any gene of interest into a cell line to understand how it affects cellular outcomes, visualize how it interacts with different cellular components, and query how cellular processes are affected by particular disease-causing mutations.

Finally, to provide the context of an organism, researchers will study biological processes in model organisms, including bacteria, yeast, plants, worms, fruit flies, fish, rodents, non-human primates, and many other organisms. Because human cells contain essentially the same molecular building blocks and pathways as these other organisms, model organisms can serve as powerful surrogates in the quest for understanding human biology and behavior. For example, certain biological processes, such as DNA replication, have been studied in detail in the single-celled organisms such as bacteria and yeast. In addition, the ability to manipulate particular genes of interest in relatively short developmental periods make worms and fruit flies powerful systems for studying normal and impaired developmental processes. Finally, as a mammalian relative, mice have served as an important system for generating animal models of human diseases and behavior. Researchers can introduce or alternatively "knock out" particular genes or cells to generate a physiological, behavioral, or disease "phenotype" of interest and examine the molecular basis for disease onset, progression, and treatment.

Advances in Basic Research Form the Building Blocks for Clinical Discovery and Improvements in Public Health

Progress in basic research does not necessarily follow a linear path from test tubes to cell culture to animal models as outlined above. Instead, basic research advances result from a continuum of collaborative interactions between research groups across multiple disciplines. The discovery of a gene that causes a diseased state in mice may spark the creation of research programs aimed at understanding the structural basis for how that gene's protein product interacts with a partner molecule as well as cellular studies to elucidate a novel molecular pathway that they regulate to generate a biological response. Conversely, the visualization of a previously unknown protein structure may provide remarkable insight on the protein's function and generate a hypothesis for how a particular mutation may generate a relevant disease model in mice. Regardless of the path taken to arrive at an incremental advance or a groundbreaking discovery, basic research lays the foundation for clinical advances that improve public health. At the heart of every clinical discovery is a body of fundamental basic knowledge that provides the impetus for setting forth a clinical hypothesis and generating the information required to safely and ethically proceed to testing in humans.

As an example of how advances in basic research build the foundation for clinical discovery and improvements in public health, NIH-supported investigators have recently discovered a novel approach for targeting the infectious bacterium *Staphylococcus aureus*; this is an important public health concern given the increasing resistance of *S. aureus* to conventional antibiotics. In 2005, a team of researchers discovered that the pigment molecule that gives *S. aureus* its golden color also serves to protect the bacteria from being killed by the human immune system following an infection.[31] Having seen this result, another NIH-funded scientist, who studies how the human body makes cholesterol, observed that the protein and molecular machinery used to make the bacterial pigment molecule is very similar to that used to make cholesterol in humans; in fact, the first steps are nearly identical.[32] Based on this observation, the two research teams, working together, went on in 2008 to demonstrate that cholesterol-lowering drugs that target a protein in humans also can be used to block *S. aureus* pigment synthesis.[33] Moreover, when these drugs are administered to mice infected with *S. aureus*, the mice are better able to kill the bacteria and overcome the infection than mice that did not receive the drug. With basic, fundamental knowledge of the proteins and pathway used to make this bacterial "virulence factor," this group of scientists has gone on to design new molecules that are more effective at blocking pigment production and reducing *S. aureus* virulence.[34] Having shown promising results in animal models, the years of collective, and initially unconnected, basic research that led to the development of this novel antimicrobial approach may offer a new strategy for reducing the public health burden of antibiotic-resistant *S. aureus* infection in humans.

Summary of NIH Activities

NIH supports a comprehensive portfolio of molecular biology and basic research aimed at understanding fundamental life processes. The results of such studies provide insights on fundamental aspects of biology and lay the foundation for other studies that will lead to ways to extend healthy life and reduce the burdens of illness and disability. In fact, each new finding serves as a building block for establishing a deeper understanding of human health and disease.

NIH supports general basic research, as well as basic research focused within a specific area or context. For example, NIH supports studies aimed at understanding the immune system in general, such as a program to better define human immune responses to infection or vaccination,[35] and also studies focused on understanding a particular aspect of the immune system, such as the immune response to specific pathogens (e.g., HIV, influenza virus, *Mycobacterium tuberculosis*) and immune-mediated diseases (e.g., allergies, type 1 diabetes, lupus, rheumatoid arthritis, primary immunodeficiency disorders).

Model Organisms and Systems

Basic research using model systems and organisms has provided the foundation of knowledge on which much of what is known about human growth and development, behavior, and the maintenance of wellness and development of disease has been learned. Research on bacteria, yeast, insects, worms, fish, rodents, primates, and even plants has shown that the basic operating principles are nearly the same in all living organisms; therefore, a finding made in fruit flies or mice may shed light on a biological process in humans. The fundamental knowledge created through studies of model systems and organisms has led to new methods for maintaining health and diagnosing and treating disease. (Also see the section on *Technology Development* in Chapter 3).

When scientists discover that a particular gene is associated with a disease in humans, one of the first things they typically do is find out what that gene does in a model organism. This often provides important clues for understanding the cause of a disease and for developing potential treatments. NIH supports the development and distribution of collections of animal systems with defects in known genes. These can be used to investigate how a particular gene found to be associated with a particular disease affects development overall and disease susceptibility and progression. For example, the NIH-sponsored National Resource for Zebrafish, *Drosophila Stock Center*, and *Caenorhabditis Genetics Center* provide the research community with well-characterized wild-type (normal) and mutant zebrafish, fruit flies, and roundworms, respectively.

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Model organisms often are especially useful for clarifying medical problems that have similar molecular causes. For example, protein clumping defects are common to several neurological disorders such as Alzheimer's, Parkinson's, and Huntington's diseases. Scientists can recreate these cellular defects in yeast, worms, and fruit flies, and then the findings can be translated into knowledge to benefit people with those diseases.

In addition to supporting studies of model organisms, NIH supports the development of a wide range of research models, particularly marine invertebrates and lower vertebrates, and the identification and development of new and improved animal models for the study of human diseases. For example, in 2008, NIH-funded researchers reported the development of a new mouse model for food allergy that mimics symptoms generated during a human allergic reaction to peanuts.[36] The animal model provides a new research tool that will be invaluable in furthering the understanding of the causes of peanut and other food allergies and in finding new ways to treat and prevent their occurrence.

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Molecular Mechanisms, Pathways, and Networks

In the human body, all biological components—from individual genes to entire organs—work together to promote normal development and sustain health. This amazing feat of biological teamwork is made possible by an array of intricate and interconnected pathways that facilitate communication among genes, molecules, and cells. While some of these biological pathways already have been discovered, many more remain to be found. Further research also is needed to understand how these pathways are integrated in humans and other complex organisms, as well as to determine how disturbances in these pathways may lead to disease and what might be done to restore disturbed pathways to their normal functions.

NIH supports a broad spectrum of research aimed at improving the molecular-level understanding of fundamental biological processes and discovering approaches to their control. In 2008, for example, NIH-supported researchers discovered that the activation of a novel set of proteins plays an important role in the development and persistence of chronic neuropathic pain conditions.[37] This discovery points scientists toward new targets for possible interventions that block the development of chronic pain. In another advance supported by NIH during FYs 2008 and 2009, scientists discovered two molecules that are important for tumor formation in head and neck cancers.[38] By uncovering how these molecules function in a key signaling pathway, scientists may be able to develop therapies that target them for the treatment of these devastating cancers. As in these studies, the goals of research supported by NIH in this area include an improved understanding of drug action; pharmacogenetics and mechanisms underlying individual responses to drugs; new methods and targets for drug discovery; advances in natural products synthesis; an enhanced understanding of biological catalysis; a greater knowledge of metabolic regulation and fundamental physiological processes; and the integration and application of basic physiological, pharmacological, and biochemical research to clinical issues.

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Cell and Molecular Biology

Growth and development is a life-long process that has many phases and functions. Much of the research in this area focuses on cellular, molecular, and developmental biology to build understanding of the mechanisms and interactions that guide a single fertilized egg through its development into a multicellular, highly organized adult organism. The eventual goal of these studies is to improve the diagnosis, treatment, cure, and prevention of human genetic and developmental disorders and diseases. (Also see the sections on *Life Stage, Human Development, and Rehabilitation* in Chapter 2 and *Genomics* in Chapter 3).

Just like a living creature, an individual cell has life stages. It is "born" (usually when its parent cell divides in two); it carries out its biological functions; it reproduces by dividing, often dozens of times; and it dies. Underlying these milestones are regular cycles, which can last from less than an hour to years or even decades. Progress through each cycle is governed by a precisely choreographed biochemical cascade involving a repertoire of molecules.

For the past several decades, NIH-supported researchers have conducted detailed studies of molecules that guide cells through division and development, methodically unraveling their biochemical identities and properties. The scientists have examined the molecules' ebb and flow throughout the cell cycle and their eventual demise as they are chemically chewed up when their job is done—until generated again for the next cell cycle. As for most life processes, when the biochemical choreography goes awry, the result can be disastrous.

Glitches in the cell cycle can lead to a host of diseases, most notably cancer, which can be defined simply as uncontrolled cell division and the failure of programmed cell death. Scientists are poised to take advantage of the wealth of basic research on the cell cycle. They are testing scores of potential anticancer drugs that aim to bolster or block cell cycle molecules. For instance, researchers also are harnessing their knowledge of the cyclical fluctuations in cell cycle molecules to predict the aggressiveness of a cancer and to tailor treatments.

Stem Cells

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell.

Given their unique regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes, heart disease, Parkinson's disease, and Alzheimer's disease. Today, donated organs and tissues often are used to replace ailing or destroyed tissue, but the need for transplantable tissues and organs far outweighs the available supply. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases. However, much work remains to be done in the laboratory and the clinic to understand how to use these cells for cell-based therapies to treat disease.

One particularly interesting research project on regenerative medicine involves a collaboration between NIH intramural researchers and scientists at Walter Reed Army Medical Center. Working together, in 2008, these scientists discovered that tissue removed from traumatic wounds, either to promote healing of orthopedic injuries or to treat war-related injuries, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells.[39] Those cells could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest stem cells from other sources.

During FYs 2008 and 2009, NIH funded multiple research projects on the basic biology of human embryonic stem cells (hESC) and has developed initiatives to support fundamental research on a new kind of stem cell, called an induced pluripotent stem cell (iPS). iPS cells are reprogrammed from adult cells to a pluripotent state remarkably like hESC. These reprogrammed cells offer a powerful approach to generating patient-specific stem cells that ultimately may be used in the clinic. (Also see the section on *Ensuring Responsible Research* in Chapter 1 for a summary of NIH activities concerning guidelines for the use of embryonic stem cells).

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Basic Immunobiology and Inflammation

The human immune system is composed of a network of specialized cells that act together to defend the body against infection by organisms such as bacteria, viruses, and parasites, and also act to prevent cancer. Unfortunately, poorly regulated immune responses can result in the development of immune-mediated diseases that include asthma, allergy, and autoimmune syndromes such as rheumatoid arthritis, multiple sclerosis, type 1 diabetes, and inflammatory bowel disease. Furthermore, it is the immune system that is responsible for the rejection of transplanted organs and tissues, which imposes the need for strong drugs to prevent rejection in transplant patients. The lack of an immune response also can be very deleterious, thus increasing susceptibility to infection. Immunodeficiency disorders can be caused by inherited flaws in the immune system, as is the case with primary immunodeficiency diseases, and by pathogens such as HIV that destroy immune cells.

Although a great deal has been learned about how the immune system operates in both health and disease, there is still more to be learned that will lead to improved and novel methods to prevent or treat human disease. Thus, NIH supports basic science studies in immunobiology (the biology of the immune system) to provide a pipeline of potential new treatments and vaccines. Research in basic immunobiology focuses on the structural and functional properties of cells of the immune system and the proteins they secrete, the interactions of immune components with other physiological systems, and the processes by which appropriate immunoregulation (regulation of the immune system) is achieved to protect the body while still preventing immune attack on self tissues.

Inflammation is triggered by molecules secreted by immune cells. Acute inflammation is triggered by damage to tissue or cells, typically by pathogens or injury. Chronic inflammation has been implicated in the etiology of multiple diseases, including asthma, atherosclerosis, cancer, cardiovascular disorders, and neurodegenerative diseases. Although significant breakthroughs have occurred in our understanding of inflammation, research is needed to further understand inflammatory processes. NIH is funding research to uncover as-yet-unknown immune mechanisms and mediators of inflammation as well as genetic factors, environmental triggers, and the relationship of inflammation to disease.

One of NIH's newer activities in this arena is the Center for Human Immunology, Autoimmunity, and Inflammation (CHI), a trans-NIH intramural initiative launched in 2008 to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiologies, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease.

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"-Omics" Approaches

Technological advances have fundamentally changed the conduct of molecular biology, making it possible to rapidly obtain information on the entire complement of biomolecules within a cell or tissue. For example, it is now possible to measure the expression of all genes (transcriptome) in a cell or tissue in less than a day, something that would have taken months if not years, just a decade ago. These advances have led to the accumulation of large datasets that scientists sift through using statistical methods, or bioinformatics, to understand how networks of cellular components work in concert to produce a state of normal health and to identify the key players that go awry as a cause or result of disease. For example, scientists may now examine the entire genome of an organism to identify genes associated with a particular trait (e.g., susceptibility to disease, developmental stage, physical trait such as height) or to compare the proteome (i.e., the entire complement of proteins) of a specific cell type with those of another (e.g., Alzheimer's brain cells vs. normal brain cells). This type of research is sometimes referred to as "hypothesis limited" because investigators cast a technological net to obtain information on the entire catalog of biomolecules within a cell or tissue before they set out to prove or disprove a specific hypothesis. (Also see the sections on *Genomics*; *Disease Registries, Databases, and Biomedical Information Systems;* and *Technology Development* in Chapter 3).

NIH has made a significant investment in genomics, transcriptomics, proteomics, and other types of "-omics" that seek to catalog a specific class or type of biomolecule, as well as bioinformatics and computational biology. This investment has led to an explosive growth in biological information, a rich resource that can be mined for clues about fundamental life processes, susceptibility to disease, and disease outcomes. This deluge of genomic information has, in turn, led to an absolute requirement for computerized databases to store, organize, and index the data and for specialized tools to view and analyze the data. NIH's National Center for Biotechnology Information (NCBI) is charged with creating automated systems for storing and analyzing knowledge about molecular biology, biochemistry, and genetics; facilitating the use of such databases and software by the research and medical community; coordinating efforts to gather biotechnology

information both nationally and internationally; and performing research into advanced methods of computer-based information processing for analyzing the structure and function of biologically important molecules. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.) The following projects provide a rich array of examples of "-omics" research supported by NIH.

The Blueprint of Life: Genomics

As exemplified by the Human Genome Project, the field of genomics aims to understand how the entire genome, or genetic composition, of a cell or an organism contributes to define development, physiology, and disease. With a map of the human genome in hand, NIH continues to support research to understand how variations in the genetic sequence among individuals contribute to health and disease. Research in the area of pharmacogenomics seeks to understand the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a beneficial response to a drug, a poor or adverse response to a drug, or no response at all. (Also see the section on *Genomics* in Chapter 3).

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Genes Don't Count for Everything: Epigenetics

While the genetic composition of an organism undoubtedly is an important determinant of health and disease, additional mechanisms are involved in interpreting the genome and guiding molecular, cellular, and developmental processes. In the emerging field of epigenetics, scientists are uncovering a complex code of chemical markers that influence whether genes are active or silent, independent of DNA sequence. While epigenetics refers to the study of a single gene or sets of genes, epigenomics refers to more global analyses of epigenetic changes across the entire genome. Epigenetic processes control normal growth and development and this process is disrupted in diseases such as cancer. Diet and exposure to environmental chemicals throughout all stages of human development, among other factors, can cause epigenetic changes that may turn certain genes on or off; research in animal models has revealed that particular parenting behaviors trigger epigenetic changes and alterations in physiological and behavioral function of offspring. Changes in genes that would normally protect against a disease, as a result, could make people more susceptible to developing that disease later in life. Researchers also believe some epigenetic changes can be passed on from generation to generation. NIH-funded scientists have demonstrated that epigenetic changes are associated with the development and growth of many types of tumors and several mental illnesses. In fact, epigenetic marks on a specific gene, the ribosomal RNA gene, have been associated with suicidal behavior. Moreover, in August 2008, NIH scientists uncovered the importance of a mammalian protein called Vezf1 in maintaining genomic integrity by regulating specific epigenetic marks on DNA at widespread sites in the genome.[40]

The NIH Roadmap Epigenomics Program, which in FYs 2008 and 2009 funded more than 2 dozen projects and consortia under a series of initiatives, aims to stimulate research on understanding the role of epigenetic regulation of gene expression in the origins of health and susceptibility to disease. It is anticipated that this program will transform biomedical research by developing comprehensive reference epigenome maps, identifying novel epigenetic marks, and developing new technologies for comprehensive epigenomic analyses. Ongoing epigenomic projects include studies on cognitive decline, atherosclerosis, and Bispenol A exposure.[41]

We Are Not Alone: The Microbiome

In addition to understanding how human genes contribute to health and disease, NIH also is interested in understanding how bacteria affect human health. The body of a healthy human adult provides a home for an enormous bacterial ecosystem, with bacterial cells outnumbering human cells by a factor of 10 to 1. Despite misconceptions that often

associate all bacteria with disease, most of the natural bacterial flora is composed of commensal—or beneficial—species that actually provide necessary cellular functions (such as the digestion of certain nutrients in the intestines). Through the NIH Roadmap, the Human Microbiome Project aims to discover the composition of microbial communities that exist in different parts of the human body and understand how these communities are associated with human health and disease. (Also see the section on *Genomics* in Chapter 3.)

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Translating the Genetic Code: Transcriptomics, Proteomics, and Metabolomics

Beyond understanding genes and their regulation, NIH also supports systemwide studies to understand what genes are actually turned on and off and when (transcriptomics). Since genes code for the proteins that carry out almost all cellular functions, understanding which genes are active and, by extension, the catalog of proteins carrying out cellular functions (proteomics) in a given cell type under particular sets of conditions, provides a picture of the molecular players involved in normal and disease states. In one example, NIH supported a comprehensive analysis of the salivary proteome—a catalog of all the proteins present in saliva. This initial description of the salivary proteome, published in 2008, provides a significant first step toward a comprehensive understanding of saliva function and provides a source of potential diagnostic and prognostic biomarkers for oral and systemic conditions.[42] In the growing field of metabolomics, researchers are using high-throughput methodologies to characterize the types and amounts of metabolic compounds present in our cells and to map the metabolic pathways and networks through which they are generated and regulated. By studying the network of chemical pathways and their chemical products, these types of studies have the capability of defining normal homeostatic and disease mechanisms. In February 2009, NIH-supported investigators reported using metabolomics to identify metabolic compounds associated with the progression from benign prostate tissue to prostate cancer.[43] Having identified pathways and compounds associated with disease progression, researchers can then use hypothesis-driven basic research experiments to further understand how particular proteins and molecules function in these pathways.

In February 2009, NIH-supported investigators reported using metabolomics to identify metabolic compounds associated with the progression from benign prostate tissue to prostate cancer.

Shape Matters: Structural Biology of Proteins

In addition to understanding the collective composition of proteins in a cell, researchers also aim to characterize their three-dimensional structures. The Structural Biology Roadmap is a strategic effort to create a "picture" gallery of the molecular shapes of proteins in the body. Of particular interest, NIH is focusing efforts on determining structures of the proteins that reside in the membrane barrier that separates the inside of the cell from the outside. These membrane proteins account for about 30 percent of the proteins in the cell and are major targets for developing therapeutic drugs to treat a particular disease by blocking, inhibiting, or activating the specific molecule. In a noteworthy example of structural advances made during FYs 2008 and 2009, NIH-supported scientists determined the three-dimensional structure of the Î²2-adrenergic receptor,[44, 45] an important target of pharmaceutical agents; knowledge of this structure adds to our fundamental understanding of how this class of proteins functions and provides insight on how to design new and improved drugs.

The Sugar Coating: Glycomics

NIH is also interested in mapping out additional molecular compounds associated with cellular function. In one field, NIH is seeking to understand the role of glycans—complex chains of sugar molecules—in various cellular functions. Glycans often are found attached to the surface of cells and to proteins found on the cell surface, and they serve important roles in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. To advance the field of

"glycomics," NIH supports programs that develop technologies for the analysis of glycans in complex biological systems and has established the Consortium for Functional Glycomics, which provides access to a technological infrastructure for glycobiology in support of basic research. Recent findings indicate that basic research on glycosylation may lead to the development of a broad spectrum antiviral. Over several years, NIH researchers discovered three antiviral proteins that bind to sugar groups commonly found on the surfaces of many viruses, which prevent the viruses from entering cells and reproducing. In 2009, investigators reported that one particularly potent antiviral protein, known as griffithsin (GRFT), appears to work well against SARS and Ebola viruses, as well as HIV.[46] So far, GRFT has only been tested in animals and cell cultures, but results are promising.

Putting It All Together with Systems Biology

With the increasing application of "-omics" and high-throughput technologies, scientists are generating massive amounts of data on the genetic and molecular basis of biological processes and responses. In an effort to put all of this information together across multiple scales, NIH researchers are turning to and pioneering the emerging field of systems biology. Systems biology draws on the expertise of biology, mathematics, engineering, and the physical sciences to integrate experimental data with computational approaches that generate models to describe complex biological systems. In addition to describing the interactions among genes, proteins, and metabolites, the models are intended to be predictive of physiological behavior in response to natural and artificial perturbations. By monitoring the effects of a perturbation in "virtual" experiments, scientists can generate hypotheses to test in cellular systems or model organisms and gain a better understanding of the molecular contributions to normal health and disease.

To support initiatives in this area, NIH has established National Centers for Systems Biology. At 10 interdisciplinary centers, NIH-funded scientists are using computational modeling and analysis to study the complex dynamics of molecular signaling and regulatory networks involved in cell proliferation, differentiation, and death; developmental pattern formation in organisms; genome organization and evolution; and drug effects on cells, organs, and tissues. The Program in Systems Immunology and Infectious Disease Modeling, a component of NIH's intramural research program, seeks to apply a systems biology approach to characterize a complex biological system—the human immune system. In this effort, researchers are seeking to develop models that enhance our understanding of the molecular basis for an immune response to infection or vaccination. In another area of systems biology research, NIH supported the construction of a "metabolic network map" for the bacterium that causes severe, chronic periodontal disease.[47] This model describes the metabolic properties of the bacterium and can be used to predict the effect of the loss of certain genes or metabolic pathways on bacterial growth rate. As the first model of this type for an oral pathogen, this metabolic network map provides opportunities to discover new antibacterial drug targets. Finally, the NIH Integrative Cancer Biology Program (ICBP) is providing new insights into the development and progression of cancer as a complex biological system. Researchers at ICBP Centers are generating and validating computational models that describe and simulate the complex process of cancer, which should ultimately lead to better cancer prevention, diagnostics, and therapeutics.

The Program in Systems Immunology and Infectious Disease Modeling in NIH's intramural research program seeks to apply a systems biology approach to characterize a complex biological system—the human immune system.

Environmental Factors that Impinge on Human Health and Disease

Just as cells respond to changes in their microscopic environment, they also are responsible for sensing and responding to environmental factors present in our "macroscopic" human world. As part of its effort to reduce the burden of human illness and disability, NIH supports basic research efforts to understand how environmental factors are detected by our bodies and how, at the molecular and cellular levels, they influence the development and progression of human diseases. The National Toxicology Program (NTP), for example, is developing innovative methods to determine which of the many chemicals that humans are exposed to are toxic, with an aim of understanding how they impart their toxic effects on human cells. In another area, researchers at the Breast Cancer and the Environment Research Centers are using genomics

and proteomics approaches to study the impact of chemicals in the environment on mammary gland development and are evaluating how environmental exposures affect important cell-cell interactions. NIH also has established research programs to investigate the relationship between exposure to heavy metals, such as mercury, in the environment and the progression and development of autoimmune disorders; understanding at the molecular level how these agents impart immune system dysfunction could offer potential therapeutic targets for treating these disorders.

Role of Basic Behavioral and Social Science Research

Recognizing the importance of behavioral and social factors in health and disease, NIH supports a broad portfolio of research in the basic behavioral and social sciences. Research in these areas provides fundamental knowledge and approaches that are essential for understanding individual and collective systems of behavior and psychosocial functioning; for predicting, preventing, and controlling illness; for developing more personalized (tailored) interventions; for enhancing adherence to treatment and minimizing the collateral impact of disease; and for promoting optimal health and well-being across the lifespan and over generations. Priority areas in basic behavioral and social sciences research include: gene-environment interactions; systems models and procedures for measurement, analysis, and classification; intergenerational transmission of behavior; biopsychosocial stress markers; and social integration and social capital.

At NIH, the mission of supporting basic behavioral and social science research is shared across ICs and OD Offices. To pursue shared opportunities and address common interests, NIH created the trans-NIH initiative known as the NIH Basic Behavioral and Social Science Opportunity Network (OppNet) in 2009. The purpose of OppNet is to pursue opportunities for strengthening basic behavioral and social sciences research while expanding and innovating beyond existing investments in these areas.

Basic behavioral and social sciences research supported by NIH is comprised of research on behavioral and social processes, biopsychosocial research, and research on methodology and measurement. Within the first category is research on behavior change, including the study of factors that shape health decision-making (e.g., cognitive, social, environmental, and developmental) and the conditions under which knowledge leads to action vs. inaction. Basic behavioral economic and decision research approaches—such as "choice architecture," which describes the way in which decisions are influenced by how the choices are presented, as well as the use of financial incentives to promote behavior change—are yielding findings that may be translated into effective interventions to change behavior and improve health. Basic research on social networks is improving our understanding of how smoking and obesity spread through socially connected individuals and provides insight into how networks might be used as vehicles to spread healthy behaviors.

Biopsychosocial research includes research on gene-environment interactions and other biobehavioral processes. The Exposure Biology Program of the NIH *Genes, Environment and Health Initiative* supports the development of tools to measure dietary intake, physical activity, psychosocial stress, and addictive substances—aspects of the behavioral and social environment—in addition to tools to measure environmental pollutants, for future use in studies of gene-environment interactions. Biopsychosocial research in humans and rodent models is elucidating how psychosocial stressors influence biological pathways involved in the growth and spread of cancer. Knowledge gained from biopsychosocial research will inform interventions to prevent, manage, and treat a variety of diseases and disorders.

The Exposure Biology Program of the NIH Genes, Environment and Health Initiative supports the development of tools to measure dietary intake, physical activity, psychosocial stress, and addictive substances—aspects of the behavioral and social environment—in addition to tools to measure environmental pollutants, for future use in studies of gene-environment interactions.

Methodological development in the behavioral and social sciences includes a new emphasis on systems science approaches. Much like the systems approaches to biology described above, systems science examines the multilevel, complex interrelationships among the many determinants of health—biological, behavioral, and social—to provide a way

to address complex problems within the framework of the "big picture." Systems science involves developing computational models to examine the dynamic interrelationships of variables at multiple levels of analysis (e.g., from cells to society) simultaneously (often through causal feedback processes), while also studying impact on the behavior of the system as a whole over time. For instance, systems science methodologies are beginning to be employed for planning and preparing against acute threats to public health such as global spread of a pandemic influenza. The Models of Infectious Disease Agent Study (MIDAS) is a collaboration of seven multi-institutional research and informatics groups focused on developing computational models of the interactions between infectious agents and their hosts, disease spread, prediction systems, and response strategies. The models will be useful to policymakers, public health workers, and other researchers who want to better understand and respond to emerging infectious diseases. Chronic diseases and risk factors for which systems science approaches would enhance our understanding and decision-making capacity include heart disease, diabetes, obesity, high blood pressure, eating behavior, physical activity, smoking, and drug and alcohol use.

Research Resources, Infrastructure, and Technology Development

In building the foundation for its broad portfolio of basic research programs, NIH also makes significant investments in the development of research resources, infrastructure, and state-of-the-art technologies that facilitate the next discoveries in biomedical and behavioral research. In line with its interest to ensure that research resources developed with NIH funding are made readily available to the research community for further research, NIH supports multiple repositories for the collection and dissemination of animal models, cell lines, and other vital biomedical research reagents. Repositories are updated continuously as resources become available and include the Mutant Mouse Regional Resource Centers, which stores, maintains, and distributes selected lines of genetically engineered mice; the National Stem Cell Bank, which makes human embryonic stem cell lines readily available; and the Beta Cell Biology Consortium, which generates animal models and antibodies that are available to the scientific community for research on type 1 and type 2 diabetes.

In addition to animal models and research reagents, NIH also supports the distribution of massive amounts of genome sequence, transcriptional profiling, and cellular structure function data for use and analysis by the research community at large. NIH continues to serve as a leading global resource for building, curating, and providing sophisticated access to molecular biology and genomic information. This includes databases such as Genbank, a collection of nearly all known DNA sequences that also provides access to the assembled Human Genome Project data. In addition to databases, NIH also provides resources for retrieving, visualizing, and analyzing molecular biology and genome sequence data online. Other examples of data sharing resources include the Biomedical Informatics Research Network, which supports the integration of data, expertise, and unique technologies to advance research on Alzheimer’s disease, autism, and other areas of neuroscience; and the Influenza Virus Resource, which provides a database of influenza virus genome sequences that may help researchers identify potential therapeutic, diagnostic, and vaccine targets. Together, it is expected that the timely sharing of research resources and data housed in these and other databases will further the research enterprise for the betterment of public health. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3).

NIH continues to support the Shared Instrumentation and High End Instrumentation Grant Programs to ensure that NIH-supported investigators have access to state-of-the-art technologies necessary to fulfill their research goals.

NIH continues to support the development and maintenance of our Nation’s research infrastructure. Since many areas of biomedical research require the use of sophisticated instrumentation, NIH continues to support the Shared Instrumentation and High End Instrumentation Grant Programs to ensure that NIH-supported investigators have access to state-of-the-art technologies necessary to fulfill their research goals. Critical to this infrastructure is support for biocontainment laboratories that allow scientists to study highly contagious, life-threatening pathogens in a safe and secure setting. NIH also continuously seeks to improve the current "state-of-the-art" in different technology areas. This is highlighted by the NIH-supported Biomedical Technology Research Centers that develop innovative technologies to aid researchers who are studying virtually every human disease. (Also see the section on *Technology Development* in Chapter 3.)

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Model Organisms and Systems

Zebrafish Help Scientists Identify Susceptibility Genes for Hearing and Balance Loss, and Drugs that May Prevent It: The sensory hair cells in the inner ear are topped with tiny, hair-like projections that detect sound or head position and movement (important for maintaining balance). Individuals demonstrate varying susceptibility to hair cell damage, which can be due to exposure to certain antibiotics, chemotherapy, other chemical agents; prolonged exposure to loud sounds; and in aging. Hair cell damage leads to hearing and balance disorders. Scientists working to understand the reason for this variability in susceptibility have used the zebrafish lateral line to model human hair cell damage. The lateral line on the fish's side contains sensory cells that detect the fish's position and motion in water. Hair cells in the lateral line function similarly to the hair cells in the human inner ear, and NIH-supported scientists exploited this to develop an important screening system. After generating fish with random mutations, the scientists subjected the mutant fish's exposed sensory cells to a potentially damaging antibiotic drug. By identifying the specific genetic mutations present in the fish and noting how the lateral line was affected by the antibiotic insult, the scientists are beginning to understand which genetic variations may be important for hearing and balance damage susceptibility. They also used the zebrafish model to study the effects of antibiotic insult combined with treatment using potentially protective substances to identify substances that seem to protect the sensory cells from damage—thus preventing potential hearing and balance disorders. The insight gained may help scientists develop personalized treatments based upon an individual's genetic makeup, and may enable prevention of some hearing and balance disorders via careful administration of protective drugs. These approaches increasingly will become important as the Nation's health care system faces the challenge of treating the aging Baby Boomer generation, many of whom already have hearing and balance problems.

→ Owens KN, et al. *PLoS Genet* 2008;4(2):e1000020. PMID: 18454195. PMCID: PMC2265478.
→ (E) (**NIDCD**)

Researchers Discover Why Mammalian Teeth Form in a Single Row: Why do mammals develop a single row of teeth whereas other vertebrates, such as sharks, can develop multiple rows of teeth? Researchers studying mutations in the genes of mice that develop teeth serving no apparent function may have solved the mystery. Most of the mutations under study caused the mice to develop the extra teeth within the space between the normal incisor and the normal first molar. Since tooth buds normally develop within this part of the developmental field but later regress, these genetic alterations did not alter the normal plane within which teeth developed. However, one particular mutation had a different result. The researchers found that a knockout mutation (i.e., elimination) of a gene known as Odd-skipped related 2 (Osr2) also resulted in the production of extra teeth, but strikingly, these teeth developed outside the usual plane, on the tongue side of the normal molars, suggesting that the mutation results in an expansion of this developmental field in the affected mice. Supporting this theory, the knockout mice (i.e., mice lacking Osr2) have spatially expanded expression of other genes

involved in tooth development. That suggests that normal Osr2 acts to restrict tooth development to within its usual, single-row plane. Previous work from this group discovered the Osr2 gene and demonstrated that it is a novel regulator of palate formation. The current study demonstrates that Osr2 function also is critical to the patterning of tooth formation and sheds light on the restriction of teeth to a single row in mammals. Osr2 function may be an important consideration for researchers seeking to grow replacements eventually for lost teeth in adults.

→ Zhang Z, et al. *Science* 2009;323:1232-4. PMID: 19251632. PMCID: PMC2650836.
→ For more information, see http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/CurrentSNIB/March/SingleRow.htm
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*
→ (E) (**NIDCR**)

Molecular Mechanisms, Pathways and Networks

New Method to Synthesize Molecules: During the past year, NIH-supported researchers discovered a new method for the preparation of a small heterocyclic molecule containing three rings that was completely unprecedented in the literature. The discovery of a ready access to novel heterocyclic scaffolds is a key contribution to innovative pharmaceutical research. Seventy analogs of this new molecule were made, and biological studies revealed potent and selective activities at G-protein coupled receptors, a biological target that accounts currently for approximately 50 percent of all new drugs.

→ Walczak MA, Wipf P. *J Am Chem Soc* 2008;130 (22):6924-5. PMID: 18461936. PMCID: PMC2754197.
→ (E) (**NIGMS**) (GPRA)

Evolutionary Analysis of Protein Domains: A group of investigators at NIH employ the latest techniques in the field of computational biology to study fundamental biological problems such as molecular evolution. Elucidating the biochemical and biological functions of protein domains is central to understanding basic life processes. (A "protein domain" is a discrete section of a protein that has its own function and can evolve independently.) Computer simulations, based on evolutionary principles, are used for the discovery, classification, evolutionary analysis, and biochemical predictions of protein domains and domain architectures. An important dimension in this type of research is discovery of "new" domains that are shared by many diverse proteins but have not been defined previously. An example of this research is the prediction of the function of the DBC1 gene, which is deleted in a prevalent form of breast cancer. Analysis of the complex domain architectures of the members of the DBC1 family suggest that they are likely to function as integrators of distinct regulatory signals, and the findings also suggest the possibility for developing new therapeutics based on soluble small molecules.

→ Anantharaman V, Aravind L. *Cell Cycle* 2008;7(10):1467-72. PMID: 18418069. PMCID: PMC2423810.
→ (I) (**NLM**)

New Targets Identified for Intervention in the Development of Head and Neck Cancers: Over the last decade, cancer researchers have made significant progress in defining the molecular pathways involved in the development of head and neck squamous cell cancer. Studies that identify and characterize "key players" hold tremendous promise for the future treatment of these devastating cancers and ultimately improve the overall survival and quality-of-life for afflicted patients. One such key player is a family of proteins known as Wnt. Aberrant activation of the Wnt pathway has been found to be associated with cancer development and progression. Wnt promotes initiation of cancer by increasing the nuclear accumulation of ß-catenin, an integral component of Wnt signaling, to activate target genes downstream. However, the mechanism of ß-catenin recruitment to the Wnt target gene promoter largely is unknown. In an elegant study, the researchers discovered that ß-catenin interacted with two other molecules (commonly called TBL1 and TBLR1), leading

to the recruitment of ß-catenin to the promoter of Wnt target genes. Decreasing TBL1 or TBLR1 via genetic knock-down did not affect the nuclear accumulation of ß-catenin, but it did inhibit ß-catenin significantly from binding to Wnt target gene promoter and the expression of Wnt target genes associated with tumor development. Moreover, depletion of TBL1 or TBLR1 inhibited invasive growth of tumor cells. These results provide fundamental knowledge about tumor genesis by revealing two new components required for nuclear ß-catenin function. Targeting these molecules can have important therapeutic implications for head and neck cancer.

→ Li J, Wang C-Y. *Nat Cell Biol* 2008;10(2):160-9. PMID: 18193033.
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*
→ (E) (**NIDCR**)

New Model Reveals Novel Molecular Strategies in the Fight to Overcome Oral Cancer: Oral and pharyngeal carcinomas are the ninth most common cancer worldwide, with more than 35,000 new patients and more than 7,500 deaths each year in the United States alone. The 5-year survival rate has improved only marginally over the past 40 years. There is an urgent need for new options for these patients. Emerging information on the deregulation of normal molecular mechanisms that result in the cancer's progression provides the possibility of new mechanisms-based therapeutic approaches for these aggressive oral malignancies. NIH scientists recently used a two-step chemical carcinogenesis model and found that the drug rapamycin exerted a remarkable anticancer activity. It decreased the tumor burden of mice having early and advanced tumors, and even brought about the regression of recurrent squamous cell skin cancers. The scientists reported that the persistent activation of mTOR, the mammalian Target of Rapamycin, occurs frequently in head and neck cancer patients and that its inhibition by rapamycin causes regression of human oral cancer tumors implanted in mice. Because chemically induced animal cancer models often better reflect the complexity of the clinical setting, the scientists developed an oral-specific chemical carcinogenesis mouse model. In this model, activation of mTOR is an early event in precancerous lesions; rapamycin treatment can halt the malignant conversion of precancerous lesions and promote the regression of advanced carcinogen-induced oral squamous cell carcinomas (SSCs). Significance: The development of this SCC carcinogenesis model demonstrates that the use of mTOR inhibitors may provide a novel molecular-targeted strategy for chemoprevention and treatment of oral squamous cell cancer.

→ Amornphimoltham A, et al. *Clin Cancer Res* 2008;14(24):8094-101. PMID: 19073969.
Czerninski R, et al. *Cancer Prevention Res* 2009;2(1):27-36. PMID: 19139015.
→ For more information, see http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/OralCancer/
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*
→ (I) (**NIDCR**)

Tumor Biology, Microenvironment, and Metastasis: The Tumor Biology and Metastasis Program supports research delineating the molecular mechanisms and signaling pathways involved in tumor progression, cell migration and invasion, angiogenesis (growth of blood vessels), lymphangiogenesis (formation of lymphatic vessels), and metastasis. Novel areas of research include the contributions of bone marrow-derived cells to tumor formation, progression, and metastasis; the role of dormant cells and their microenvironment; the role of host tissue microenvironment in organ-specific metastasis; characterization of the heterogeneity within the tumor microenvironment; and the characterization of cancer as a systemic disease. The Tumor Microenvironment Network (TMEN) investigates mechanisms of tumor-stroma interactions in human cancer. (Stroma is the connective tissue that supports or surrounds other tissues and organs.) In addition to delineating the role of host stroma in carcinogenesis, TMEN investigators are generating novel reagents that can be shared with the research community. The Cancer Immunology/Hematology Program supports research on the cellular and molecular characterization of tumor stem cells, which are minor populations of tumor cells that may be responsible for recapitulating all the cell types in a given tumor and causing metastasis due to their unique self-renewal properties. In FY 2008, NIH sponsored two RFAs on tumor stem cells aimed at enhancing synergistic research between basic scientists and translational scientists working on tumor stem cells. In addition, a program announcement for Stem Cells and Cancer was

released to stimulate efforts to isolate and characterize tumor stem cells from a large spectrum of tumors to understand better the progression of malignant disease.

→ For more information, see http://tmen.nci.nih.gov
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-019.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-020.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-165.html
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NCI**)

Glucosamine and Chondroitin Fare No Better Than Placebo in Slowing Structural Damage of Knee Osteoarthritis: Osteoarthritis affects an estimated 27 million Americans, and researchers are seeking ways not only to treat pain, but also to address the loss of cartilage—a hallmark of the condition. The two-part Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), funded by NIH, investigated whether this dietary supplement can treat pain and diminish structural damage associated with knee osteoarthritis. In the primary study (GAIT I), combined glucosamine/chondroitin sulfate did not provide significant relief among study participants overall, although a smaller subgroup with moderate to severe pain did show significant relief. The 18-month GAIT II ancillary study followed cartilage loss in GAIT participants with moderate or severe osteoarthritis in one or both knees, comparing the effects of glucosamine and/or chondroitin sulfate with placebo. In GAIT II, glucosamine and chondroitin—together or alone—appeared to fare no better than a placebo in slowing loss of cartilage in osteoarthritis of the knee, measured by joint space width as seen on x-rays. Interpreting the study results is complicated, however, because participants taking placebo had a smaller loss of cartilage than predicted. In addition to its findings on the effects of dietary supplements taken by many Americans for osteoarthritis, GAIT II provided new insights on osteoarthritis progression, techniques for measuring loss of joint space width, and characteristics of osteoarthritis patients who may respond best to glucosamine/chondroitin.

→ Sawitzke AD, et al. *Arthritis Rheum* 2008;58(10):3183-91. PMID: 18821708.
→ For more information, see http://nccam.nih.gov/news/2008/092908.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NCCAM, NIAMS**)

Promising Approaches to Treating Chronic Pain: Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can result in addiction, tolerance, and physical dependence, all of which may undercut their value in some patients. Thus, an area of enormous need is the development of potent analgesics with diminished abuse liability for treating chronic pain. In response, NIH has implemented an aggressive and multidisciplinary research program that is yielding tangible results, which stand to revolutionize the field of pain management. At the molecular level, cannabinoid (CB) research has shown that it is possible to activate the CB system selectively to provide analgesia with minimal or no effects on mental function, and no abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different (heteromeric) receptors. Targeting them could provide a vastly expanded range of pharmacotherapeutics. This approach has already ushered in the development of promising designer molecules that can block pain more selectively and safely. At the cellular level, active research on non-neuronal brain cells has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their proinflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of other analgesic drugs. At the brain circuit level, a new approach has been developed to harness the brain's intrinsic capacity to train itself through a strategy in which subjects "learn" how to regulate pain by viewing, and then controlling, images of their own brains in real time.

→ Varga EV, et al. *Curr Mol Pharmacol* 2008;1(3):273-84. PMID: 20021440.
Ferre S, et al. *Trends Neurosci* 2007;30(9):440-6. PMID: 17692396.

Daniels DJ, et al. *Proc Natl Acad Sci U S A* 2005;102(52):19208-13. PMID: 16365317. PMCID: PMC1323165.
Ledeboer A, et al. *Expert Opin Investig Drugs* 2007;16(7):935-50. PMID: 17594181.
deCharms RC. *Trends Cogn Sci* 2007;11(11):473-81. PMID: 17988931.

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*

→ (E) (**NIDA**, NINDS)

Peripheral Neuropathies: NIH funds studies focused on understanding the genetic basis and molecular and cellular mechanisms of many peripheral neuropathies, including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, inherited neuropathies such as Charcot-Marie-Tooth, inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy, and rare forms of peripheral neuropathy. Other notable projects include a natural history study of diabetic neuropathy, projects to improve the efficiency and effectiveness of diagnosis for various peripheral neuropathies, and a Phase III clinical trial to treat Familial Amyloidotic Polyneuropathy. In August 2008, a pair of program announcements was released to promote translational research in neuromuscular disease. Diseases included in these program announcements are those that affect the motor unit—the motoneuron, its process (axon), and the skeletal muscle fiber that is innervated by the neuron—such as peripheral neuropathy, amyotrophic lateral sclerosis, and muscular dystrophy. This unique structure-function framework provides a coordinated approach for therapeutic development in a subset of neurological diseases that share many common features, including the peripheral neuropathies.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*

→ (E) (**NINDS**, NIDDK)

Understanding the Roles of Non-Neuronal Cells in Neuropathic Pain Provides New Targets for Intervention: Chronic pain caused by nerve injury, called neuropathic pain, is difficult to treat because we do not yet fully understand the biological mechanisms underlying its development and persistence. Most pain-relieving medications for chronic pain target nerve cells, yet it is becoming clear that non-nerve (non-conducting) cells also play an important role in some chronic pain conditions. Matrix metalloproteases (MMPs) are enzymes that break down the medium surrounding tissue cells. MMPs also activate several pro-inflammatory proteins that stimulate the non-nerve conducting function of of the supportive glial cell. Scientists are wondering if neuropathic pain and inflammation are linked by a common mechanism involving MMP activation. Researchers found that a specific matrix metalloprotease, MMP9, showed increased activity soon after nerve injury, which stimulated the glial cells in the spinal cord, but this increased activity declined after several days. A different enzyme, MMP2, also was increased, but at later times after injury; this increase led to activation of another nerve-supportive cell in the spinal cord. The research showed that the pain response of nerve-injured animals were blocked early by inhibitors of MMP9 or later by inhibitors of MMP2. These findings suggest an important role for MMP9 in the onset of chronic neuropathic pain conditions, and for MMP2 in the persistence of those conditions. The results also demonstrate the complex interplay between nerve cells and several non-nerve cells. This research describes a novel set of molecules involved in neuropathic pain, and points scientists toward new targets for possible interventions to short-circuit the onset and persistence of chronic pain conditions.

→ Kawasaki Y, et al. *Nat Med* 2008;14(3):331-6. PMID: 18264108. PMCID: PMC2279180.

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*

→ (E) (**NIDCR**)

From Genes to Therapy in Neurogenetic Disorders: Neurofibromatosis (NF) and tuberous sclerosis complex (TSC) are neurogenetic disorders that cause tumors on nerves, in the brain, and on other organs. Although the tumors are benign, consequences of their size and location can be serious. Clinical manifestations can include seizures, autism, and cognitive disability. NIH support led to identification of the genes underlying these disorders, and recently has enabled investigators to uncover disease mechanisms that point to strategies for therapeutic development. One NF study revealed that an NF1 gene mutation in bone marrow cells (which infiltrate peripheral nerves prior to NF tumor development) is necessary for tumor growth. Activation of c-kit, a molecule implicated in some cancers and targeted by the cancer drug Gleevec, enables release of the cells from bone marrow to stimulate neurofibroma growth. In this study, Gleevec treatment prevented formation and reduced neurofibroma size and activity. If clinical trials prove successful, Gleevec could become the first approved NF treatment. In TSC, genetic mutations cause deregulation of an anti-tumor molecule, mTOR, which is a known target of rapamycin (a drug currently used to treat organ transplant rejection). In previous studies, rapamycin reduced the size of brain and kidney tumors in TSC patients. Recent NIH-supported research in mice revealed that rapamycin, via the mTOR pathway, inhibited TSC-induced brain enlargement and mortality, prevented seizures, and improved cognitive ability in mice, results which have led to clinical trials now in Phase III. Rapamycin also alleviated seizures in a rat model of epilepsy, which may shed light on TSC-associated neurological diseases, including autism and epilepsy.

→ Ehninger D, et al. *Nat Med* 2008;14(8):843-8. PMID: 18568033. PMCID: PMC2664098.
Meikle L, et al. *J Neurosci* 2008;28(21):5422-32. PMID: 18495876. PMCID: PMC2633923.
Yang FC, et al. *Cell* 2008;135(3):437-48. PMID: 18984156. PMCID: PMC2788814.
Zeng LH, et al. *J Neurosci* 2009;29(21):6964-72. PMID: 19474323. PMCID: PMC2727061.
Zeng LH, et al. *Ann Neurol* 2008;63(4): 444-53. PMID: 18389497.
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E) (**NINDS**, NCI, NICHD, NIMH)

Insights into the Molecular Interplay Governing Formation of Cranial Sensory Ganglia: The developmental biology underlying sensory nerve development is fascinatingly intriguing. Take the trigeminal ganglion, which is responsible for touch, pain, and temperature sensation for most of the face. How do precursor cells self-organize in the embryo to produce an anatomically correct sensory network connecting to the central nervous system? Many of the answers are wired into the molecular circuitry of two transient embryonic cell types called neural crest cells and ectodermal placodes. They interact during embryonic development to differentiate into the nerve cells that form the trigeminal ganglion. But virtually nothing is known about the molecular interplay that mediates this interaction. It is a biological puzzle with no known pieces. Now NIH grantees have introduced the first two pieces of the puzzle. They demonstrated in animal studies that the cranial subtype of neural crest cells express the protein Slit1 on their surface during their programmed migration to the trigeminal-forming ectodermal placodes. Meanwhile, as the trigeminal placode cells follow their developmental program, they express on their surface the Robo2 protein, which is the receptor for the Slit1 protein. The Robo2-Slit1 connection, like fitting a hand in a glove, mediates the interaction of neural crest and trigeminal placode cells during the formation of sensory ganglia. When the scientists disrupted one or both molecular signals, the resulting sensory ganglia were abnormal. The teams' findings are important to understanding the mechanisms that regulate formation of the sensory nervous system and thus provide potential targets for identifying the causes of congenital sensory disorders involving the neural crest cell population.

→ Shiau CE, et al. *Nat Neurosci* 2008;11(3):269-76. PMID: 18278043.
→ For more information, see http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/Archive/archive2008/April/TrigeminalGanglion.htm
→ For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18278043?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIDCR**)

Neurobiology of Appetite Control: NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. For example, the sight of food has been found to induce different responses in the brains of patients following weight loss; these differences are due to changes in levels of the hormone leptin. Researchers also discovered that rats susceptible to becoming obese from a high-calorie diet have fewer neural connections in the brain in the hypothalamus (the part of the brain that has a key role in weight regulation) compared to normal rats. Additionally, a factor secreted by the small intestine in response to dietary fat intake has been found to enter the brain and suppress appetite in rats. More recently, six new genetic regions associated with obesity were identified and found to be in or near genes expressed in the brain. To highlight further the connection between brain function and obesity, a trans-NIH workshop on neuroimaging in obesity research was held to share data and experiences with functional neuroimaging approaches to study brain involvement in various aspects of obesity such as weight gain and loss, and the neurotransmitters and brain structures associated with energy balance, hunger, and decision-making. A recent funding opportunity announcement was issued to foster new research using neuroimaging approaches to enhance understanding of food intake and energy expenditure in the context of obesity. This research has implications for new therapies for obesity.

→ Rosenbaum M, et al. *J Clin Invest* 2008;118(7):2583-91. PMID: 18568078. PMCID: PMC2430499.
Bouret SG, et al. *Cell Metab* 2008;7:7(2):179-85.PMID: 18249177. PMCID: PMC2442478.
Gillum MP, et al. *Cell* 2008;135(5):813-24.PMID: 19041747. PMCID: PMC2643061.
Willer CJ, et al. *Nat Genet* 2009;41(1):25-34. PMID: 19079261. PMCID: PMC2695662.
→ For more information, see http://www3.niddk.nih.gov/fund/other/neuroimaging2008/
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/rfa-dk-08-009.html
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDDK**)

Not Only In Your Mouth—Your Gut Can Taste, Too: Sugars consumed in food affect blood sugar levels differently than sugars given intravenously. Scientists have been examining sugar-binding molecules in the gut lining to determine why this happens. While the tongue has been known as the taste organ of the body, NIH-funded scientists recently have identified taste receptors in the human gut. Their data suggest that the human gut detects sugars in food through these taste receptors, and uses this information to turn up the production of blood sugar-regulation hormones, including the hormone that regulates insulin release. Individuals that have difficulty detecting and regulating sugar can gain weight more easily and/or develop other metabolic problems, including diabetes. The discovery of taste receptors in the lining of the gut may help scientists develop drugs that are specific to the gut taste receptors to treat weight problems and diabetes, two very significant public health issues.

→ Jang HJ, et al. *Natl Acad Sci USA* 2007;104(38):15069-74. PMID: 17724330. PMCID: PMC1986614.
Margolskee RF, et al. *Proc Natl Acad Sci USA* 2007;104(38):15075-80. PMID: 17724332. PMCID: PMC1986615.
→ (E/I) (**NIDCD**, NIA)

Grape Seed Extract May Help Neurodegenerative Diseases: Tauopathies—a group of neurodegenerative conditions such as Alzheimer's disease—have been linked to the build-up of "misfolded" tau proteins in the brain. (Tau proteins are associated with microtubules, which help to regulate important cellular processes.) In light of previous studies indicating that grape-derived polyphenols may inhibit protein misfolding, an NIH-funded research center examined the potential role of a particular grape seed polyphenol extract (GSPE) in preventing and treating tau-associated neurodegenerative

disorders. In one study, the researchers found that this GSPE reduced Alzheimer's-type neuropathology and cognitive decline in a mouse model of Alzheimer's disease and inhibited an Alzheimer's-linked process called cerebral amyloid deposition. In another study, the researchers used a variety of analytical techniques to clarify further how the GSPE produces its effects. The results of their preclinical study showed that GSPE interferes with the generation of tau protein aggregates and also disassociates preformed aggregates. Thus, GSPE may affect processes critical to the onset and progression of neurodegeneration and cognitive dysfunctions in tauopathies. The studies' findings, together with indications that this GSPE is likely to be safe and well-tolerated in people, support further exploration and development of GSPE as a therapy for Alzheimer's disease.

→ Ho L, et al. *J Alzheimers Dis* 2009;16(2):433-9. PMID: 19221432. PMCID: PMC2800939.
Ono K, et al. *J Biol Chem* 2008;283(47):32176-87. PMID: 18815129. PMCID: PMC2583320.
Wang J, et al. *J Neurosci* 2008 Jun 18;28(25):6388-92. PMID: 18562609. PMCID: PMC2806059.
→ For more information, see http://nccam.nih.gov/research/results/spotlight/031209.htm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E) (**NCCAM**)

Cell and Molecular Biology

Basic Research on Human Embryonic Stem Cells: Research on human embryonic stem cells (hESC) promises to elucidate critical events in early human development and may revolutionize customized regenerative medicine. Since FY 2007, NIH has funded five Program Projects on the basic biology of hESC and has developed initiatives to support fundamental research on a new kind of stem cell, called induced pluripotent stem cells (iPS). iPS cells are reprogrammed from adult cells to a pluripotent state remarkably like hESC. These reprogrammed cells offer a powerful approach to generating patient specific stem cells that ultimately may be used in the clinic. NIH sponsored the third in a series of workshops on research and future directions in human embryonic stem cell research in September 2009.

→ For more information, see http://www.nigms.nih.gov/Initiatives/StemCells
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIGMS**)

Scientists Demonstrate Hematopoietic Stem Cells' Role in Forming the Stem Cell Niche: Stem cells are important in all multicellular organisms because they have the ability to develop into different kinds of specialized cells. Outside of the organism, researchers can grow stem cells in specific cultures and observe the development of specialized cells. Blood-forming stem cells, known as hematopoietic stem cells (HSCs), are controlled by the hematopoietic stem cell niche, which is located in the bone marrow. Bone-forming cells called osteoblasts are known to play a central role in establishing the HSC niche; however, it is unclear whether HSCs in turn control the differentiation of stem cells that become osteoblasts. Although such interactions in the niche have been proposed, at present there is insufficient direct experimental evidence to define the relationship between HSCs and osteoblast formation. In this work, a group of investigators addressed the role of HSCs in the differentiation of osteoblasts. Using mice, they co-cultured HSCs with stem cells that become osteoblasts, and demonstrated that HSCs can indeed affect the differentiation of cells into osteoblasts. Further, the investigators found that the specialization or differentiation into osteoblasts could be influenced by the age and physical condition of the mice. These findings suggest that HSCs may serve as an important therapeutic target for controlling bone formation and repair. In particular, it should be possible to develop therapeutic agents that specifically target HSCs for treatment of a variety of bone defect such as osteoporosis, nonhealing bone and tooth defects, and congenital bone abnormalities.

→ Jung Y, et al. *Stem Cells* 2008;26(8):2042-51. PMID: 18499897.
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIDCR**)

Stem Cells and Regenerative Medicine: Stem cells are able to renew themselves and generate progeny that differentiate into more specialized cells. They play critical roles in organism development, and some are essential for normal homeostasis and tissue repair. NIH has made a significant investment in stem cell research. One NIH-supported study showed that the sex of cells in a subpopulation of muscle-generating stem cells in adult mice can influence their capacity to repair tissue considerably. This finding could lead to future therapies for various diseases, including muscular dystrophy. A collaboration between NIH Intramural researchers and those at Walter Reed Army Medical Center discovered that waste tissues from surgery, removed to promote healing of orthopaedic injuries and war-traumatized muscle, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells. They could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest cells. NIH has partnered with the Department of Defense on an initiative to speed treatments to wounded soldiers abroad, and civilian trauma victims and burn patients in the United States. This collaboration has resulted in the establishment of the new Armed Forces Institute of Regenerative Medicine (AFIRM). The AFIRM-led program will focus on regrowing fingers, repairing shattered bones, and restoring skin to burn victims with genetically matched skin, to pave the way for commercial products in the near future. Hair follicles are useful models for organ regeneration. Recent discoveries have been made in the molecular processes that govern the growth of hair follicle stem cells, which are a source for newly formed hair follicles.

→ Deasy BM, et al. *J Cell Biol* 2007 Apr 9;177(1):73-86. PMID: 17420291. PMCID: PMC2064113.
Jackson WM, et al. *J Tissue Eng Regen Med* 2009 Feb;3(2):129-38. PMID: 19170141.
Plikus MV, et al. *Nature* PMID: 18202659. PMCID: PMC2696201.
Horsley V, et al. *Cell* 2008 Jan 25;132(2):299-310. PMID: 18243104. PMCID: PMC2546702.
Nesti LJ, et al. *J Bone Joint Surg Am* 2008;90(11):2390-8. PMID: 18978407. PMCID: PMC2657299.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cell_sex_and_stem_cell.asp
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/progenitor_cells.asp
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
→ (E/I) (**NIAMS**, NIA, NIAID, NIBIB)

NIH Stem Cell Task Force: In 2002, NIH established a Stem Cell Task Force to continually monitor the state of this rapidly evolving area of science. The purpose of the Task Force is to enable and accelerate the pace of stem cell research by identifying rate-limiting resources and developing initiatives to overcome these barriers to progress. The Task Force seeks the advice of scientific leaders in stem cell research about moving the stem cell research agenda forward and exploring strategies to address the needs of the scientific community. Since 2002, under the leadership of the Task Force, NIH has supported a wide array of scientific programs designed to foster research on all types of stem cells, including human embryonic stem cells (hESCs), and actively is working to fund research in this blossoming field. For example, the Task Force has stimulated NIH-supported research by initiating Infrastructure grants to scale-up and characterize the hESCs eligible for Federal funding under prior presidential policy, established a National Stem Cell Bank to make these hESC lines readily available, developed training courses to teach stem cell culture techniques, and encouraged new investigator-initiated research through various means. The Task Force also is responsible for implementing Executive Order (EO) 13505, issued by President Obama on March 9, 2009. EO 13505 authorizes the Secretary of Health and Human Services, through the Director of NIH, to support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law. The NIH Guidelines for Human Stem Cell Research were issued on July 7, 2009.

→ For more information, see http://stemcells.nih.gov/policy/taskforce/
→ For more information, see http://stemcells.nih.gov/policy/2009guidelines.htm
→ (E/I) (**NIDCD, NINDS**, FDA, NCI, NCRR, NHLBI, NIDCR, NIDDK, NIGMS, OD, OER, ORWH, OSP/OSPA)

Bone Marrow Stromal Cells Help Fight Sepsis: Sepsis is a serious medical condition that affects 18 million people per year worldwide, and is characterized by a generalized inflammatory state caused by bacterial infection. Widespread activation of inflammation and blood clotting pathways leads to multiple organ failure, collapse of the circulatory system (septic shock), and death. In the last few years, it has been discovered that bone marrow stromal cells (BMSCs, also known as mesenchymal stem cells) are potent modulators of immune responses. In this study, BMSCs were administered before or shortly after inducing sepsis by puncturing the intestine to determine whether BMSCs injected into the circulation would have a beneficial effect in preventing or attenuating septic shock. Infusion of BMSCs significantly decreased sepsis-induced mortality and increased organ function in an animal model. The effects appear to be mediated by the production of Prostaglandin E2 when BMSCs are activated during the early stages of sepsis. Prostaglandin E2 subsequently induces the recipient's macrophages to produce substantially more IL-10, a factor that dampens the inflammatory response, which if left unabated, leads to death. This is the first determination of a mechanism by which BMSCs modulate the immune response in an animal model of sepsis. As many people die of sepsis annually as die from heart attacks. A new treatment or preventative regimen desperately is needed. Since the animal model suggests that the BMSCs need not be isolated from the same individual as will receive them, it is possible that cells isolated from nonrelated donors could be prepared and stored for use in patients with high risk for sepsis.

→ Nemeth K, et al. *Nat Med* 2009;15(1):42-9, PMID: 19098906. PMCID: PMC2706487.
→ For more information, see http://www.nature.com/nm/journal/v15/n1/abs/nm.1905.html
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Technology Development*
→ (I) (**NIDCR**)

Effects of Storage on Transfused Red Blood Cells: In 2009, NIH initiated a basic and translational research program to identify the molecular and cellular changes that occur during red blood cell unit preparation and storage and to evaluate the effects of storage lesion elements from red blood cell units on the blood vessel wall, host cells, and tissue oxygenation. Recent data suggest that liberal blood transfusions in certain settings are associated with an increase in morbidity and mortality compared to more restrictive strategies, and that transfusion of blood stored for longer periods of time may not be as beneficial as transfusion of "fresher" blood. This program should provide information for improving red blood cell transfusion therapy and clinical outcomes in transfusion recipients.

→ (E) (**NHLBI**)

Smart Coatings for Implanted Biomaterials: A major limitation on the longevity of vascular grafts and implanted materials stems, not from failure of the graft or material itself, but typically, from the body's rejection in the form of blood clots or refusal to integrate with surrounding tissue. Recently, new classes of polymer-based biomimetics that resemble the cell surfaces of healthy blood vessels have demonstrated excellent resistance to platelet adhesion, a major problem for implanted materials in contact with blood. These biomimetic polymers have undergone successful preliminary clinical testing, and the same approach now is being used to develop biomimetic coatings resembling other types of human tissue. This technology recently was acquired by a major medical implant manufacturer.

→ Kumar AM, et al. *J Am Chem Soc* 2008;130(4):1466-76.PMID: 18177047. PMCID: PMC2536642.
Larsen CC, et al. *Biomaterials* 2007;28(24):3537-48. PMID: 17507089. PMCID: PMC2034336.
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIBIB**)

New Therapeutic Target for Macular Degeneration and Diabetic Retinopathy Discovered: Neovascularization is the term used to describe the growth of abnormal new blood vessels. In some diseases, such as age-related macular degeneration or diabetic retinopathy, neovascularization mistakenly activates and becomes a major pathologic feature. The abnormal vessels leak fluid and serum, which damages the light-sensitive photoreceptor cells in the retina, causing severe and irreversible vision loss. NIH-sponsored research is focused on understanding the pathways that inhibit and promote neovascularization. Previous studies have established that a protein called vascular endothelial growth factor (VEGF) spurs neovascularization, and several therapies have been developed to prevent the abnormal activation of VEGF. A recent NIH-supported study reported the discovery of Roundabout4 (Robo4), a protein that stabilizes the existing vasculature and prevents neovascularization by inhibiting VEGF activity. Robo4 is among a family of Roundabout proteins that previously were found to act as guidance receptors for developing neurons in the nervous system. That Robo4 plays a different and central role in controlling neovascularization represents a breakthrough that may lead to new treatments to prevent or delay the sight-threatening consequences of vascular eye diseases.

→ Jones CA, et al. *Nat Med* 2008;14(4):448-53. PMID: 18345009.
→ For more information, see http://www.nature.com/nm/journal/v14/n4/full/nm1742.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NEI**)

Cell Senescence and Aging: Cell senescence is a mechanism prominent in aging processes and widely considered as an anti-cancer preventive or treatment therapy. Studies focus on such topics as senescence induced by the Ras gene and its potential to halt or slow tumor progression, the role of the retinoblastoma protein pRb in cellular senescence and the development of a wide range of cell types and associated tumors, telomere attrition, the role of oxidative stress, epigenetic regulation, and DNA damage and repair. NIA-supported studies on Werner syndrome (a condition characterized by accelerated aging in children) and the role of the WRN protein in telomere metabolism are improving our understanding of basic cellular mechanisms that act to suppress development of specific aging characteristics and cancer.

→ This example also appears in Chapter 2: *Cancer* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E/I) (**NIA**)

Cooperative Study Group for Autoimmune Disease Prevention: The Cooperative Study Group for Autoimmune Disease Prevention (CSGADP) was established in 2001 by NIH and its cosponsor the Juvenile Diabetes Research Foundation International as a collaborative network of investigators who focus on understanding immune system dysfunctions that contribute to the development of autoimmune disease (AD), with an emphasis on type 1 diabetes. NIH renewed the Study Group in 2006. It consists of six participating centers that support preclinical research, innovative pilot projects, and clinical studies. Of note, the centers initiated and supported the "Roadmap to Inflammation in the NOD (nonobese diabetic) Mouse" project to identify and characterize genes and proteins involved in the development of diabetes, and study the mechanisms by which diabetes develops. One notable finding suggested by this study is that the development of type 1 diabetes can be characterized by specific differences in how normal genes and gene variants are turned on and off during disease progression. In addition, researchers found patterns of coordinated gene expression that may prove useful as biomarkers of disease onset or progression. Another study, in press, identifies an unusual form of a gene whose expression in specific immune system tissues is associated with type 1 diabetes in both mice and humans.

→ Kodama K, et al. *Clin Immunol* 2008;129(2):195-201. PMID: 18801706. PMCID: PMC2592195.
→ For more information, see http://fathmanlab.stanford.edu/roadmap_study_design.html
→ This example also appears in Chapter 2: *Autoimmune Diseases*
→ (E) (**NIAID**, NIDDK)

Basic Research on Type 1 Diabetes: NIH vigorously supports basic research on type 1 diabetes. For example, the Beta Cell Biology Consortium (BCBC) collaboratively pursues research relevant to the development of therapies for type 1 and type 2 diabetes, including studying pancreatic development, exploring the potential of stem cells as a source for making islets, and determining mechanisms underlying beta cell regeneration (cells that are the source of insulin production). The BCBC has generated research resources, such as animal models and antibodies, which are available to the scientific community. NIH also has launched initiatives to develop artificial pancreas technology for people with type 1 diabetes. One initiative solicited proposals from the small business community on the development of new technologies to advance progress toward an artificial pancreas. NIH also launched the Type 1 Diabetes Pathfinder Awards, to fund new investigators pursing innovative research on type 1 diabetes and its complications. Research supported through this program focused on areas such as cell replacement therapy, islet encapsulation, and diabetic wound healing.

→ For more information, see http://www.betacell.org
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-09-001.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-08-012.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-08-013.html
→ For more information, see http://www2.niddk.nih.gov/Funding/FundingOpportunities/RFA/RFA_T1D_Pathfinder_Announcement.htm
→ This example also appears in Chapter 2: *Autoimmune Diseases*
→ (E) (**NIDDK**, NIBIB, NICHD)

Lupus: There have been significant advances in identifying disease risk genes for systemic lupus erythematosus (lupus) in recent years. Genome-wide association, linkage analysis, and direct sequencing have revealed genetic variations in lupus patients for molecules involved in immune mechanisms and regulation, inflammation, and vascular cell activities. The disease affects women disproportionately, with female lupus patients outnumbering males nine to one. African American women are three times as likely to get lupus as Caucasian women, and it also is common more in Hispanic, Asian, and American Indian women. These results are being replicated in distinct racial and ethnic populations. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects. Another critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by government agencies, private foundations, and industry. The numerous genes uncovered in these studies reflect the complex expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene specifically is associated with severe forms of lupus that include kidney disease, but not skin manifestations. Methods to analyze patients' blood samples are being developed to group disease-specific variations in gene expression according to pathogenic mechanisms. This system may be used to predict flares of lupus activity in the future and guide individualized treatment. Lupus risk genes also have been discovered on the X chromosome and reproduced in animal models of the disease. These important findings shed light on the female predominance of lupus.

→ Edberg JC, et al. *Hum Mol Genet* 2008 Apr 15;17(8):1147-55. PMID: 18182444.
Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), et al. *Nat Genet* 2008;40(2):204-10. PMID: 18204446.
Taylor KE, et al. *PLoS Genet* 2008;4(5):e1000084. PMID: 18516230. PMCID: PMC2377340.
Chaussabel D, et al. *Immunity* 2008;29(1):150-64. PMID: 18631455. PMCID: PMC2727981.
Smith-Bouvier DL, et al. *J Exp Med* 2008;205(5):1099-108. PMID: 18443225. PMCID: PMC2373842.
Scofield RH, et al. *Arthritis Rheum* 2008;58(8):2511-7. PMID: 18668569.
Jacob CO, et al. *Proc Natl Acad Sci U S A* 2009;106(15):6256-61. PMID: 19329491. PMCID: PMC2669395.
→ This example also appears in Chapter 2: *Autoimmune Diseases*, Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Genomics* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAMS**, NCI, NCRR, NHLBI, NIAID, NIDCR, NINDS)

Asthma Exacerbations: In FY 2005, NIH began a basic and clinical research initiative to improve understanding of the causes of asthma exacerbations and to facilitate the development of more effective treatments to control asthma symptoms. Twelve projects have been funded under this initiative. NIH is assessing the progress of the initiative through an ongoing GPRA goal—"to identify and characterize two molecular pathways of potential clinical significance that may serve as the basis for discovering new medications for preventing and treating exacerbations, by 2014."

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-04-029.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NHLBI**) (GPRA)

Understanding the Progression from a Skin Disorder to Asthma in Children: NIH-funded researchers investigating basic biochemical mechanisms involved in development have discovered a mechanism that can explain how 50-70 percent of young children affected with the skin rashes of atopic dermatitis (a type of eczema) eventually become asthmatic. The process involves the overproduction of a specific signaling molecule by inflamed skin cells that can trigger the hypersensitivity characteristic of asthma in lung cells. This mechanism and possible ways to prevent this "atopic march" and the development of asthma in general are being actively evaluated in animal models as well as in early human studies.

→ For more information, see http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1000067
→ This example also appears in Chapter 3: *Genomics*
→ (E) (**NIGMS**)

Immunological Factors in Autoimmune Disease: T Helper Cells: T helper cells are a category of immune cells that orchestrate many complex mechanisms in the immune system by receiving molecular signals and, in return, releasing other molecules that control activities of other cells. As a result, these recipient cells are stimulated, or inhibited, from damaging tissues or destroying pathogenic invaders. Studies in recent years have identified a number of T helper cell (Th) subsets that have fairly specific responses to immune system molecules, and are pivotal to attacks against pathogens, as well as autoimmune reactions—when the immune system aberrantly attacks the body it is supposed to protect. NIH-supported researchers have found that one Th subset (Th17) releases molecules that start a cascade of inflammatory events. The effects of Th17 and other pro-inflammatory cells are balanced by another Th subset, T regulatory cells (Tregs), which dampen inflammation. Job's syndrome is a rare immune disorder, characterized by recurrent and often severe bacterial and fungal infections. Due to a genetic mutation affecting a complex biochemical pathway, patients with Job's syndrome lack interleukin 17 (IL17), the molecule that stimulates Th17 cells. As a result, their immune systems fail to protect them from infections, which have the potential to become life-threatening. On the other hand, patients with psoriasis, an autoimmune skin disease, have high levels of IL17 and very active Th17 cells, which drive inflammation in the skin, leading to scaly, damaged tissue. Additional studies have revealed ways that the body might inactivate Tregs. By understanding the details of failures in biochemical pathways in disease states, scientists may begin to identify ways to correct them therapeutically.

→ Lowes MA, et al. *J Invest Dermatol* 2008;128(5):1207-11. PMID: 18200064.
Milner JD, et al. *Nature* 2008;452(7188):773-6. PMID: 18337720.
→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2008/job_ma.htm
→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2008/08_13b.asp
→ This example also appears in Chapter 2: *Autoimmune Diseases*
→ (E/I) (**NIAMS**, NCRR)

New Program to Focus on Better Defining Human Immune Profiles: In 2009, NIH requested applications for a new research program designed to build on recent advances in immune profiling to measure the diversity of human immune responses to infection or vaccination. Grantees will use a variety of modern analytical tools that will define molecular signatures of specific infections, vaccines, or immune adjuvants, as well as describe steady-state human immune status by a number of parameters. This program is a critical component of the NIH immunology research portfolio. This initiative supports studies that characterize human immune cells and their products isolated from diverse subsets of the population after vaccination, infection, or treatment with adjuvants. NIH will create a grantee consortium that will develop and manage a comprehensive database that consolidates and disseminates information for the scientific community and develop new assays and bioinformatics tools to facilitate productivity. This program, originally intended as an FY 2011 initiative, began 1 year early with ARRA funding.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-040.html
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Autoimmune Diseases*
→ (E) (**NIAID**) (ARRA)

Solving One of Immunity's Puzzles: NIH scientists recently identified a protein required for the crucial interactions between T and B cells that lead to production of antibodies and long-lasting immunity to infectious diseases. T cells and B cells interact to form cellular centers, where B cells proliferate and produce antibodies to fight off invading microbes. This process is crucial to normal immune function and resistance to infectious disease. Researchers demonstrated that a protein, SAP, mediates interactions between T and B cells. Specifically, the team found that T cells lacking SAP do not bind strongly to the B cells they would otherwise recognize. This in turn prevents B cells from receiving crucial signals they need to help build antibody-secreting cells. This malfunction leads to the poor immune response observed in patients with X-linked lymphoproliferative disease, a rare disorder affecting newborn boys.

→ Qi H, et al. *Nature* 2008;455(7214):764-9. PMID: 18843362. PMCID: PMC2652134.
→ For more information, see http://www.genome.gov/27528397
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E, I) (**NHGRI, NIAID**)

Developing New Adjuvants to Boost Vaccine Effectiveness: Adjuvants activate the body's innate immune system, a prerequisite for effective responses by the adaptive immune system—antibody-producing B cells and antigen-specific T cells. In 2004, NIH launched the "Innate Immune Receptors and Adjuvant Discovery" initiative in response to the growing need to boost the effectiveness of vaccines against potential agents of bioterrorism and emerging infectious diseases. The initiative encouraged the discovery of novel adjuvants that stimulate the innate immune response through proteins known as pattern recognition receptors, which the innate immune system uses to identify microbial pathogens. To build on the success of this program, NIH initiated the Adjuvant Development program in 2008. Four groups were funded to advance identified adjuvants toward licensure for human use in vaccines against diseases such as influenza and tuberculosis, as well as infection with West Nile virus. The "Innate Immune Receptors and Adjuvant Discovery" initiative was reissued—inviting new grant applications—in FY 2009 to continue the generation of potential adjuvant candidates. The research focus on adjuvants yielded a major science advance in 2008 when several groups of NIH-supported investigators discovered that alum activates the innate immune system by stimulating clusters of proteins called inflammasomes, found inside certain cells. This new information should provide keys to better understanding adjuvant function and should facilitate the design of new vaccine adjuvants.

→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2008/alum_vaccine.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIAID**)

Improving Transplantation Outcomes: Organ transplantation prolongs survival and greatly improves quality of life for children and adults suffering from a wide range of congenital and acquired diseases. Yet, despite advances in transplantation, normal life expectancy and health-related quality of life are not restored fully by organ transplantation. To improve the outcomes of organ transplantation, NIH supports the Clinical Trials in Organ Transplantation (CTOT) initiative, a cooperative, multisite consortium to develop and implement interventional and observational clinical studies, accompanied by mechanistic studies.

In one notable CTOT study, NIH-supported investigators developed a regimen that included transplantation of both kidney and bone marrow from the same donor and use of immunosuppressive therapies prior to and just after transplantation. Nine to 14 months after the transplant, investigators were able to discontinue all immunosuppressive medications with this regimen in four of the five patients, without subsequent rejection of the kidney. In another study, NIH-supported investigators studied whether acute graft rejection was associated with changes in the expression of genes involved with the adaptive immune response. They measured levels of microRNAs in healthy transplanted kidneys and in transplants undergoing rejection. The team found a pattern of six microRNAs that could distinguish healthy kidneys from those in the process of being rejected. These results suggest that microRNAs may be a useful measurement for assessing human kidney transplant status. If the rejection signature appears early enough, doctors one day may be able to treat patients before organ damage occurs and to better tailor immunosuppressive therapy to the individual patient.

- → Kawai T, et al. *N Engl J Med* 2008 Jan 24;358(4):353-61. PMID: 18216355. PMCID: PMC2819046.
- → For more information, see http://www.immunetolerance.org/
- → This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- → (E) (**NIAID**, NHLBI, NIDDK)

'Omics' Approaches

Discovery of Novel Epigenetic Marks in Mammalian Cells: The NIH Roadmap Epigenomics Program aims to accelerate the promise of epigenetics into applications that affect human health and a wide range of common complex human diseases by fostering the development of novel resources for research in this field. Epigenetics refers to various modifications to DNA, its associated proteins, or overall chromosome structure that influence whether genes are active or silent, independent of the DNA sequence. Research supported by this program will characterize the "epigenome," a catalog of the stable epigenetic modifications or "marks" that occur in the genome (and which may differ in different types of cells) and its impact on health and disease. One component of the program is an initiative to support research to identify novel epigenetic marks in mammalian cells and assess their role in the regulation of gene activity. It is anticipated that the results of these studies will be translated quickly to global epigenome mapping in human cells (conducted by the Epigenomics Roadmap Program's Reference Epigenome Mapping Centers). The eight research grants funded by this component of the program are expected to yield results that could have a significant impact on our understanding of gene regulation in mammals. In the long term, advances in these areas will enhance our ability to investigate, diagnose, and ameliorate human disease with a significant epigenetic component. For instance, NIH plans to build on these studies to examine the role of epigenomics in diabetes complications and to study effects of the intrauterine environment on the development of diabetes. Other research will examine epigenetic markers of beta cell differentiation.

- → For more information, see http://nihroadmap.nih.gov/epigenomics/initiatives.asp
- → This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Genomics*
- → (E) (**NIDDK**, Common Fund - all ICs participate)

Regulation of Gene Expression by Chemically Marking DNA: Studies by NIH intramural scientists of how genes are turned on (expressed) or off have provided insight into gene regulation and the overall organization of the genome. For example, a recent study indicated the importance of a mammalian protein called Vezf1 in maintaining the integrity of the genome. This protein previously had been identified by research on an "insulator" element—a segment of DNA that marks boundaries in the genome and allows neighboring genes to be regulated independently. Research on insulator elements—found in fruit flies, chickens, and mammals—has provided great insight into the molecular mechanisms used by the cell to turn on certain genes while keeping other genes turned off. In studies of Vezf1, the scientists discovered that deletion of the gene encoding the Vezf1 protein in a mouse embryonic stem cell line led to loss of specific chemical marks on the DNA at widespread sites in the genome. This type of chemical mark, known as DNA methylation, is a signal used by the cell to turn a gene off. The scientists also demonstrated that the loss of DNA methylation observed when Vezf1 was deleted was due to a decrease in the amount of a specific protein that puts this mark on the DNA. Therefore, Vezf1 is required for the DNA methylation pattern in these cells. Continued studies of insulators and their associated proteins will lead to further understanding of the regulation of genes, an essential process for health and development.

→ Gowher H, et al. *Genes Dev* 2008;22(15):2075-84. PMID: 18676812. PMCID: PMC2492749.
→ This example also appears in Chapter 3: *Genomics*
→ (I) (**NIDDK**)

Scientists Accomplish Initial Catalogue of the Human Salivary Proteome: Secretions from the major salivary glands (parotid, submandibular, and sublingual) contain many peptides and proteins. They contribute to saliva's important roles in maintaining oral health, including antimicrobial, lubricating, buffering, and digestive properties. Salivary gland disorders, which result in severe dry mouth, compromise quality of life because they often lead to decay and periodontal diseases, mucosal infections, halitosis, taste impairment, and difficulties in swallowing and speaking. Saliva is a complex fluid; over the years, a number of salivary proteins have been reported but a systematic approach to catalogue all the proteins present in saliva was only initiated in 2004. NIH supported three teams of investigators to conduct the first comprehensive analysis of the salivary proteome. After samples were collected and analyzed, the data were standardized and integrated, yielding a salivary proteome that comprises 1,166 proteins. Of these proteins, 152 parotid and 139 submandibular/sublingual proteins were identified by all 3 research groups; these proteins form the core proteome. Most proteins identified were extracellular or secretory proteins, and involved in numerous molecular and cellular processes. A significant number of proteins represented in the salivary proteome also have been found to exist in the plasma or tear proteomes. This initial catalogue of the salivary proteome is a significant first step toward a comprehensive understanding of what the functions of saliva are, and how salivary composition is dependent on physiological variations, including on health and disease. This proteome could be the source of potential diagnostic and prognostic biomarkers for oral and systemic conditions.

→ Denny P, et al. *J Proteome Res* 2008;7:1994-2006. PMID: 18361515.
→ This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*
→ (E) (**NIDCR**)

Study Finds Unexpected Bacterial Diversity on Human Skin: One of the NIH Roadmap initiatives, the Human Microbiome Project (HMP) is a trans-NIH program that aims to expand upon traditional microbiology and discover what microbial communities exist in different parts of the human body and how they might change with disease. In a healthy adult, microbial cells far outnumber those of the human host, but remarkably little has been known until now about how these microbes behave in the body. HMP makes use of a metagenomic approach that reveals data about entire human-associated microbial communities. In 2009, data gathered by a trans-NIH team revealed unexpected bacterial diversity on human skin that, it is hoped, will lead to advances in understanding a range of disorders, such as eczema, psoriasis, and acne.

→ Grice EA, et al. *Science* 2009;324(5931):1190-2. PMID: 19478181.
→ For more information, see http://nihroadmap.nih.gov/hmp/index.asp
→ This example also appears in Chapter 3: *Genomics*
→ (I) (**NHGRI**, Common Fund - all ICs participate, NCI)

Glycomics Technology Development, Basic Research, and Translation into the Clinic: Glycans are ubiquitous complex carbohydrates found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules is thus critical for basic and clinical research across the spectrum of health and disease, but widely is regarded as one of the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- Biomedical Technology Research Centers develop and share cutting-edge technologies for analysis of carbohydrates in complex biological systems.
- Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.
- Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
- A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.

→ For more information, see http://www.ncrr.nih.gov/glycomics
→ For more information, see http://www.functionalglycomics.org
→ This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
→ (E) (**NCRR**, NCI, NHLBI, NIGMS, NINDS)

Reference Epigenome Mapping Centers: The Reference Epigenome Mapping Centers (REMCs), one of the Roadmap Epigenomics initiatives, are developing resources in reference epigenomes that the field has been requesting for the last 5 years, as indicated by recommendations made at several workshops and conferences focused on epigenetics and human health and disease. The funded centers form a network collaborating to provide comprehensive maps of all known epigenetic marks across a set of mutually agreed-upon reference cell types. This consortium, with input from advisors, will identify the most appropriate cell populations and determine standardized methods for growing or acquiring the cells so that data can be compared and integrated maps can be generated. The network of REMCs will produce comprehensive, high resolution, experimental data on epigenetic marks in specific cell populations, such as high-quality, pluripotent human embryonic stem cells, other human differentiating stem cells, and differentiated cell types including human cell types relevant to complex diseases of high public health significance. In addition, it will provide an informatics pipeline to generate high-quality reference epigenome maps from the centers' data; facilitate additional data analyses, in collaboration with the Epigenome Data Analysis and Coordinating Center, to integrate data from maps generated by REMCs from a specific cell type for different epigenetic marks; and conduct ancillary studies to develop limited data on functional aspects of epigenetic control of gene activity.

→ For more information, see http://nihroadmap.nih.gov/epigenomics/
→ For more information, see http://cancerres.aacrjournals.org/cgi/reprint/65/24/11241
→ For more information, see http://www.landesbioscience.com/journals/epigenetics/article/heindelEPI1-1.pdf
→ This example also appears in Chapter 3: *Genomics*
→ (E) (**NIEHS, NIDA**, Common Fund - all ICs participate)

Systems Biology

Systems Biology and Systems Genetics: The Integrative Cancer Biology Program (ICBP) provides new insights into the development and progression of cancer as a complex biological system. Teams of researchers at ICBP Centers are integrating the disciplines of biology, medicine, engineering, math, and computer science (e.g., computational biology). ICBP Centers use a spectrum of innovative technologies such as genomics, proteomics, and molecular imaging to generate and validate computational and mathematical models. These in silico models describe and simulate the complex process of cancer, from the basic cellular processes through tumor growth and metastasis, and allow researchers to run "virtual" experiments, which ultimately should lead to better cancer prevention, diagnostics, and therapeutics. The centers have produced more than 35 computational models, developed a validated siRNA library of cancer genes, and created a set of nationally distributed breast cancer cell lines that reflect the heterogeneity of human breast cancer. Equally important to our understanding of cancer is systems genetic research (systems biology + genetics). Networks of genes can be found and their associations tested and quantified with parallel association studies on relevant human populations.

→ For more information, see http://icbp.nci.nih.gov/
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NCI**)

National Centers for Systems Biology: Systems biology promotes tight integration of experimental and computational approaches to solving complex problems. Currently, NIH-funded researchers at10 interdisciplinary Centers are using computational modeling and analysis to study the complex dynamics of molecular signaling and regulatory networks involved in cell proliferation, differentiation, death, and response to environmental changes; developmental pattern formation in organisms; genome organization and evolution; and drug effects on cells, organs, and tissues. The Centers advance their research fields and provide training for the next generation of computationally skilled scientists.

→ For more information, see http://www.nigms.nih.gov/Initiatives/SysBio
→ (E) (**NIGMS**)

Computational Modeling of Regulatory Processes: Phosphorylation, the addition of a phosphate group to a protein or other molecule, is a common mechanism of cellular processes. Proteins may contain more than 1 site of phosphorylation, and, interestingly, many key regulatory proteins are phosphorylated at 10 or more different sites. NIH-funded researchers recently have introduced novel methods, based in the sophisticated branch of mathematics known as "algebraic geometry," into a computational model of phosphorylation, giving them a new technique to explore a variety of processes related to cancer and other diseases. This advance exploits a mathematical construct named for the Austrian mathematician Wolfgang Grobner (1899-1980), and demonstrates how long-established findings in fields such as abstract mathematics can be brought to bear in the context of biological research. In this case, the mathematics allows the computational biologists to work around putting a precise numerical value to every detail of the model, thus greatly simplifying their efforts to perform computational experiments. It is anticipated that these simplifying methods, based on an area of mathematics previously far removed from work in the life sciences, will be widely applicable to modeling of many biological processes.

→ Manrai AK, Gunawardena J. *Biophys J* 2008; 95(12):5533-43. PMID: 18849417. PMCID: PMC2599844.
→ (E) (**NIGMS**)

Metabolic Network Model of a Human Oral Pathogen: The bacterium *Porphyromonas gingivalis* causes severe, chronic periodontal disease. Recently NIH-supported researchers constructed a complex metabolic network map for *P. gingivalis* with which to model the metabolic properties of all genomically identified components of the system. The scientists used a technique known as flux-balance analysis (FBA) to construct the model, which consisted of 679

metabolic reactions involving 564 metabolites. There was significant correlation between the model's predictions and the bacterium's experimentally observed metabolism. The true power of this model became apparent when "virtual knockouts" were employed to predict the effect of the loss of certain genes or metabolic pathways on growth rate, and the model very effectively predicted disturbances affecting biosynthesis of large molecules known as lipopolysaccharides. This is the first description of a model of this type for an oral periodontal pathogen. Still in their infancy, metabolic network models are a logical extension of genome sequence data. They can provide the ability to perform virtual metabolic modeling of organisms with limited or no in vivo experimental histories. These models also could be applied to highly interdependent mixed microbial communities, including the oral microbiome, ultimately resulting in new biomedical applications. Such modeling greatly increases opportunities to discover new antibacterial drug targets. These studies provide new molecular targets for therapeutic drugs; they also can suggest the molecular mechanisms for virulence, intracellular persistence and survival, and ability of the bacteria to survive stresses from the (in this case, human) host defense mechanisms.

→ Mazumdar V, et al. *J Bacteriol* 2009;191(1):74-90. PMID: 18931137. PMCID: PMC2612419.
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Technology Development*
→ (E) (**NIDCR**)

Environmental Factors

Centers for Neurodegenerative Science: NIH has awarded three Centers for Neurodegeneration Science program grants to conduct research that combines human studies with basic mechanistic research to understand how environmental factors contribute to the origins, progression, treatment, and prevention of neurodegenerative diseases. The three projects will focus on investigating Parkinson's disease (PD). PD is linked to pesticide exposure, mitochondrial damage, and altered storage of dopamine. One project will look at how environmental and genetic factors interact in PD pathogenesis and search for biomarkers that will help identify people at risk for developing PD. A second project will investigate the importance of the ubiquitin-proteasome system, microtubules, and aldehyde dehydrogenase disruption by pesticides in conferring vulnerability to dopamine neurons. An integrated, multidisciplinary approach will be used to identify agricultural pesticides that are able to disrupt the same cellular pathways shown to alter the viability of dopaminergic neurons and determine whether these pesticides increase the risk of PD. The third project will focus on proteins known to be related to PD with the goal of determining how chemical reactions lead to damaging modifications of these proteins. Clinical implications will be explored through biomarker development and a screen to identify compounds that can preserve protein function by reducing free radical stress. The knowledge generated by these projects will provide therapeutic targets for disease intervention and prevention strategies.

→ Yu T, et al. *Bioinformatics* 2009;25(15):1930-6. PMID: 19414529. PMCID: PMC2712336.
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Choo YS, Zhang Z. *J Vis Exp* 2009 Aug 19;(30). pii: 1293. doi: 10.3791/1293. PMID: 19692941.
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E) (**NIEHS**)

Environmental Epigenetics: Key Mechanisms for Environmental Effects on Gene Function and Disease: Increasing evidence demonstrates that epigenetic mechanisms—cellular regulatory processes that influence the expression of genes without affecting DNA sequence—play important roles in the pathogenesis of disease. Epigenetic regulation of genes is critically important in normal developmental biology and disease development/progression, and epigenetic modifications

can be influenced by environmental exposures (this may be an important mechanism for gene/environment interactions). An early NIH grant program called Environmental Influences on Epigenetic Regulation has resulted in some groundbreaking research on understanding these processes and their roles in health and disease. We know that environmental exposures early in development affect the risk of diseases and dysfunctions that occur in adulthood, many years later. Evidence is growing that exposures *in utero* exert their effects through epigenetic modifications such as DNA methylation (a chemical change to DNA that is associated with silencing gene expression). A recent study in yellow agouti mice demonstrated that maternal exposure to bisphenol A shifted the coat color of the offspring by decreasing methylation in a regulatory portion of the DNA sequence upstream of the coat-color gene. Moreover, maternal dietary supplementation with either folic acid or a phytoestrogen (genistein) inhibited the ability of bisphenol A to reduce DNA methylation. These and other results highlight the importance of this growing area of research for our ability to understand developmental pathogenesis and to design effective interventions.

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→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIEHS**)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects

adipose tissue and alters hormonal control of sexual maturation. Endocrine distruptors, irradiation, and psychosocial elements also will be studied for effects.

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→ For more information, see http://www.bcerc.org/

→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Genomics* and Chapter 3: *Clinical and Translational Research*

→ (E) (**NIEHS**, NCI) (GPRA)

National Toxicology Program/Tox21: Tox21 is a collaboration on the research, development, validation, and translation of new and innovative test methods that will better determine the toxicity of chemicals to which humans are or might be exposed. A central component is the exploration of novel high-throughput screening assays using human cells to evaluate mechanisms of toxicity. Program success will result in toxicity testing methods that are less expensive, provide higher throughput, and are better able to predict toxic effects in humans. As a result, Tox21 will increase the government's ability to evaluate large numbers of chemicals that currently lack adequate toxicological evaluation, while reducing the use of animals in regulatory testing.

→ (I) (**NIEHS**) (GPRA)

Testing for Reproductive Tumors in the National Toxicology Program's Carcinogenesis Bioassay: Perinatal Dosing: The National Toxicology Program (NTP) evaluates substances for a variety of health-related effects. Two-year studies in laboratory rodents remain the primary method by which chemicals or physical agents are identified as having the potential to be hazardous to humans. In 2006, NTP convened a workshop on Hormonally Induced Reproductive Tumors, Relevance of Rodent Bioassays to discuss the adequacy of rodent models used in the 2-year bioassay for detecting reproductive tumors. The workshop recommended that in utero and lactational exposures could be added to the chronic bioassay depending upon what is known about the mode of action. For detecting tumor types such as testicular germ cell tumors, this recommendation was especially strong. In utero and lactational exposures should be considered for mammary tumor studies if there are any developmental effects associated with a substance under study that involved

endocrine tissues, steroid receptor binding, a change in mammary gland morphology, or altered timing of vaginal opening. NTP has conducted such perinatal exposures on cancer bioassays in the past, but only when there was special justification for such a design to be adopted. A new default design in which dosing will start in pregnancy and be continued throughout life or to the end of a 2-year period now has been adopted unless there is a good scientific reason not to undertake such a study. NTP has initiated studies to obtain data for constructing physiologically based pharmacokinetic (PBPK) models in rodents and nonhuman primates. It is planning studies to explore the long-term consequences of perinatal exposure to Bisphenol A to understand the potential impact to humans of the developmental changes reported in numerous laboratory animal studies. It is hoped that the PBPK models will link information from rodent studies with primate studies, and potentially with human outcomes.

→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*
→ (O) (**NIEHS**)

Mercury and Autoimmunity: The causes of autoimmune diseases remain unknown although genetic and environmental factors are believed to play major roles in susceptibility. NIH supports research projects investigating heavy metal-induced autoimmune diseases. The Mercury Induced Autoimmunity Project is working on the role that interferon-gamma plays in the development of induced murine systemic autoimmunity. Another NIH-supported project is investigating links between mercury (Hg) exposure and autoimmune heart disease. This project will assess programming changes that occur during the innate immune response to infection following exposure to Hg, with an overall effect on the progression of Coxsackievirus-induced autoimmune heart disease in mice, and apply the biomarkers from the studies in animals to a Hg-exposed human population in Amazonian Brazil. Another project is investigating the effect of Hg on the neuroimmune system. Studies will investigate the effects of Hg on production of autoantibodies to brain antigens. Antibodies to brain antigens have been demonstrated in patients with different neurological diseases, including neuropsychiatric lupus, Parkinson's disease, schizophrenia, and autism spectrum disorders. An ongoing project is working on development and uses mouse models to understand the relationships between immune system dysfunction and perinatal exposure to environmental toxicants in the development of neurobehavioral disorders such as autism. Mice from this project will be used to assess the effects of perinatal exposure to low levels of methyl mercury (MeHg) on abnormal brain development and behavior mediated by the immune system. These studies should allow insight into the mechanism of induction of immune dysfunction and point to a possible means of therapeutic intervention.

→ Havarinasab S, et al. *Clin Exp Immunol* 2009;155(3):567-76. PMID: 19077085. PMCID: PMC2669534.
→ This example also appears in Chapter 2: *Autoimmune Diseases*
→ (E) (**NIEHS**)

Bisphenol A Exposure and Effects: More than 90 percent of the U.S. population is exposed to low levels of BPA. Exposures may occur through use of polycarbonate drinking bottles and the resins used to line food cans. The NIH National Toxicology Program's (NTP's) Center for the Evaluation of Risks to Human Reproduction conducted an evaluation to determine whether current levels of exposure to BPA present a hazard for human reproduction and/or development. Following this evaluation of existing literature, the NTP expressed "some concern" for effects on the brain, behavior, and prostate gland based on developmental effects reported in some laboratory animal studies using BPA exposures similar to those experienced by humans. NIH is working to address and support research and testing needs identified during the NTP evaluation to understand any potential risks for humans from BPA exposure. In collaboration with scientists at the FDA National Center for Toxicological Research, the NTP has designed and begun studies to evaluate similarities and differences in how rats metabolize BPA in relation to nonhuman primates, and to further understand the long-term health consequences from exposures to low levels of BPA during rodent development. In addition, NIH is providing grant support to the extramural community for studies that focus on investigating possible long-term health outcomes from developmental exposure or chronic exposures to environmentally relevant doses of BPA.

Collectively, these studies should address research gaps, reduce uncertainties, and provide perspective regarding any potential risk that BPA poses for public health.

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→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research*

→ (I) (**NIEHS**)

Basic Behavioral and Social Science Research

NIH Basic Behavioral and Social Science Opportunity Network: NIH Basic Behavioral and Social Sciences Opportunity Network (OppNet) is a new trans-NIH initiative that will identify and support research in the basic behavioral sciences. Basic research in the behavioral and social sciences examines fundamental mechanisms and patterns of behavioral and social functioning. Examples include research on how people remember, how innovative practices spread, and the effects of brain processes on behavior. Basic behavioral and social sciences research (bBSSR) involves both human and animal studies and spans the full range of scientific inquiry, from processes at the intra-individual level ("under the skin"), to mechanisms "outside the skin" that explain inter-individual, group-, organizational-, community-, and population-level patterns of collective behavior. The mission to support basic behavioral science is shared across NIH ICs. Initiated in September 2009, OppNet will provide a means for integrating NIH's assessment of its bBSSR investments, ensuring that opportunities in relevant areas of science are addressed, and that effective mechanisms are in place to advance these sciences. The initiative will support targeted initiatives of general relevance to the NIH mission, drawing from a common pool of funds.

→ (E) (**NIA, NIGMS, OBSSR**, FIC, NCCAM, NCI, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIMH, NINDS, NINR, NLM, OAR, ODP, ORWH)

Facilitating Interdisciplinary Research via Innovation in the Behavioral and Social Sciences: An NIH Roadmap Funding Opportunity Announcement (FOA), Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences, was released. Using a modified Exploratory/Developmental (R21) mechanism, this FOA solicits applications to develop new and innovative measures, methods, and technologies that support the integration of human social and/or behavioral science with other disciplines across varying levels of analysis. Supported projects have included: creation of tools to measure sun exposure and vitamin D, models of spinal cord injury, and an Internet-based system for providing feedback to teachers and consultants on the

school readiness and mental health of children. Several national conferences have been planned in relation to this initiative, including *Facilitating Interdisciplinary Research: Methodological and Technological Innovation in the Behavioral and Social Sciences* (October 2009).

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-004.html
→ For more information, see http://nih.blhtech.com/roadmap09/
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIDA, OBSSR**, Common Fund - all ICs participate)

CISNET—A Resource for Comparative Effectiveness Research: The Cancer Intervention and Surveillance Modeling Network (CISNET) represents a quantum leap forward in the practice of modeling to inform clinical and policy decisions. While contemporary science has enabled the collection and analysis of health-related data from numerous sectors, enormous challenges remain to integrate various sources of information into optimal decision-making tools to inform public policy. Collaborative work on key questions promotes efficient collecting and sharing of the most important data and critical evaluation of the strengths and weaknesses of each resource. Providing results from a range of models, rather than a single estimate from one model, brings credibility to the process and reassures policymakers that the results are reproducible. CISNET is a consortium of NIH-sponsored investigators who use modeling to improve understanding of the impact of cancer control interventions (e.g., prevention, screening, and treatment) on incidence and mortality trends. The consortium's work informs clinical practice and recommended guidelines by synthesizing existing information to model gaps in available knowledge. CISNET provides a suite of models that are poised to determine the most efficient and cost-effective strategies for implementing technologies in the population. Four groups of grantees focus on breast, prostate, colorectal, and lung cancers using statistical simulation and other modeling approaches. Their models incorporate data from randomized controlled trials, meta-analyses, observational studies, epidemiological studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of these interventions.

→ For more information, see http://cisnet.cancer.gov/
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NCI**)

Support for Collaborative Science: In FY 2009, NIH launched the Administrative Supplements for Collaborative Science (SCS) program. These supplements are intended to enhance ongoing research by stimulating and supporting new multidisciplinary collaborations among NIGMS grantees and other members of the scientific community. The program has proved to be quite popular. NIH received 217 applications for the three submission dates in FY 2009, and plans to fund at least 32 applications from Institute funds. NIGMS intends to support additional meritorious applications with funds received from the American Recovery and Reinvestment Act of 2009.

→ For more information, see http://www.nigms.nih.gov/Initiatives/Collaborative/SCS.htm
→ (E) (**NIGMS**) (ARRA)

NIH Committee on the Science of Behavior Change (SOBC): A key national goal, at the scientific and policy level, is to eliminate preventable diseases and their associated disabilities and premature deaths. To achieve this goal, the science of behavior change increasingly is being recognized as a critical area for research. While NIH historically has invested in biobehavioral research, SOBC is a crucial step to coordinate, leverage, and advance these efforts. The SOBC initiative examines topics that span the continuum of behavior change and across disciplines. The SOBC goals include the identification of new and productive paradigms for SOBC research—paradigms that will facilitate the synthesis, integration, and application of SOBC research; that will help to bridge the distances that often separate investigators and

disciplines; and that will inform and identify future research directions and initiatives. On June 15-16, 2009, NIH brought together experts in the fields of basic and applied behavioral sciences, genetics, economics, and methodology with the goal of advancing an NIH-wide agenda on the science of behavior change. The main topics of discussion were the acquisition and prevention of behavior, changing existing behavior, and maintenance of behavior. The SOBC working group will use ideas generated from the meeting to develop new interdisciplinary initiatives in behavior change research.

→ For more information, see http://nihroadmap.nih.gov/documents/SOBC_Meeting_Summary_2009.pdf
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NINR, NIA**, DPCPSI, FIC, NCCAM, NCI, NHGRI, NHLBI, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIGMS, NIMH, NINDS, OBSSR)

Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging: NIH supports 13 Roybal Centers whose objective is to improve the health, quality of life, and productivity of middle-aged and older people by facilitating translation of basic behavioral and social science to practical outcomes by developing new technologies and stimulating new "use-inspired" basic research in the behavioral and social sciences. Roybal investigators have made several key discoveries. For example: One Center has developed tools and technologies for identifying older adults at risk for automobile crash involvement, and is working with industry partners to develop and disseminate products based on these tools. Another Center has developed two evidence-based interventions from its in-depth work on physical activity for older adults. One program, Fit and Strong!, is targeted to older adults with lower extremity osteoarthritis, and one is targeted to older adults with developmental/intellectual disabilities (primarily Down syndrome). A Roybal investigator has developed instruments for self-efficacy appropriate for use with older adults with developmental/intellectual disabilities; these have been adopted internationally. Finally, a Center has developed a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Other companies have used this model to develop related products, and the model has spurred several new grant-funded research projects, including the development of a new medication tracker for older adults.

→ For more information, see http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/roybals.htm
→ This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
→ (E) (**NIA**)

NIH Revision Awards for Studying Interactions Among Social, Behavioral, and Genetic Factors in Health: NIH issued three program announcements with review (PARs) to support competitive supplements for NIH grantees to study how interactions among genetic and behavioral/social factors influence health and disease. NIH is committing $7.9 million to support 11 applications submitted in response to these announcements, which will enable the addition of a genetics/genomics component to ongoing behavioral or social science research projects. The knowledge gained by such research will improve our understanding of the determinants of disease as well as inform efforts to reduce health risks and provide treatment.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/par-08-065.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-066.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-067.html
→ For more information, see http://obssr.od.nih.gov/scientific_areas/Genes_Beh_Environ/index.aspx
→ This example also appears in Chapter 3: *Genomics*
→ (E) (**OBSSR**, NCCAM, NCI, NEI, NHGRI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIMH, NINDS, NINR, ODP/ODS)

Genes Involved in the Regulation of Sensitivity to Alcohol: Low doses of alcohol are stimulating in both humans and animals while higher doses have sedating effects. Sensitivity to alcohol, however, varies across individuals and low sensitivity to alcohol is a risk factor for the development of alcohol dependence in humans. Research with individuals who have a high family history of alcoholism seeks to understand how low response to alcohol contributes to dependence and how it can be used to predict risk for future alcohol problems. Research with animals is useful in identifying the mechanism(s) underlying the level of sensitivity to alcohol. Recently, a study with fruit flies implicated the Epidermal Growth Factor Receptor (EGFR) signaling pathway in regulating sensitivity to alcohol. Importantly, FDA-approved medications that inhibit EGFR increase alcohol sensitivity in mice and decrease alcohol intake in rats, suggesting that these drugs may offer therapeutic opportunities for treatment of alcohol use disorders in humans.

→ Corl AB, et al. *Cell* 2009;137(5):949-60. PMID: 19464045.
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→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIAAA**)

The Role of Development in Drug Abuse Vulnerability: NIH supports animal, clinical, and epidemiological research across the lifespan to examine how developmental stage may influence drug abuse vulnerability or protection. The discovery of a protracted period of brain changes during early development and beyond has been critical to understanding the role of brain maturation in decision-making processes and responses to stimuli, including early (e.g., in utero) exposure to drugs. Adolescence has emerged as a particularly vulnerable period, during which an immature brain circuitry can translate into a preponderance of emotional reactivity (vs. higher cognitive control) that gives rise to the impulsive characteristics of many teenagers. This in turn may lead to dangerous risk-taking, such as experimenting with drugs that ultimately can lead to addiction. Using both animal models and clinical research, scientists are beginning to understand how environmental variables can play a key role in shaping brain maturation trajectories. In this regard, imaging, genetic, and epigenetic tools are helping interpret the effects of myriad environmental influences, such as quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics on brain development and behavior. In addition, the field of social neuroscience is harnessing the power of multidisciplinary approaches to tease apart these multilevel phenomena to better understand, for example, the neural mechanisms of peer pressure, the connections between chronic stress and risk of drug abuse initiation, and the impact that different early rearing environments can have on gene expression and behavior.

→ For more information, see http://www.nida.nih.gov/tib/prenatal.html
→ For more information, see http://www.nida.nih.gov/scienceofaddiction/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIDA**, NICHD) (GPRA)

New Genetics/Epigenetic Tools Shed Light on Addiction: NIH-supported research is taking full advantage of expanding databases and fast technologies to identify links between genetic variations and disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms underlying complex diseases like addiction, which genes strongly influence. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as "gene chips" (e.g., the neurexin gene has been found to play a role in drug addiction). Applying these tools to addiction and other brain disorders advances our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient's genetic profile. To complement these efforts, NIH is investing in the equally important field of epigenetics, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the

deleterious long-term changes to brain circuits from drug abuse. For example, using a powerful new technique known as ChIP-on-chip to monitor epigenetic changes correlated with gene activity, investigators recently have mapped the genomic effects of chronic cocaine use in the reward center of the mouse brain. Such analyses provide needed information about which genes are altered by cocaine and can point to new targets for medications development. Epigenetic discoveries also can inform ways to smartly alter environmental factors so as to decrease the risk for drug abuse and addiction.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-015.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-016.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-003.html
→ For more information, see http://nihroadmap.nih.gov/epigenomics/initiatives.asp
→ For more information, see http://nihroadmap.nih.gov/commonfundupdate.asp
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Genomics* and Chapter 3: *Technology Development*
→ (E/I) (**NIDA**, NCI, NIAAA, NIMH) (GPRA)

A Multidisciplinary Approach to Tobacco Addiction: Tobacco addiction is the number one preventable public health threat, with enormous associated morbidity, mortality, and economic costs. Cigarette smoking—powerfully addictive mainly because of the key ingredient nicotine—is the greatest preventable cause of cancer, accounting for at least 30 percent of all cancer deaths, 87 percent of lung cancer deaths, and nearly 80 percent of deaths from chronic obstructive pulmonary disease, according to CDC. CDC also reports that these leading causes of death could become relatively uncommon in future generations were the prevalence of smoking substantially reduced. In that vein, NIH-supported research has led to major advances in critical areas that together could greatly enhance our ability to either prevent or mitigate the impact of tobacco addiction. Convergent genomic studies recently have uncovered several genes previously not associated with nicotine reward or addiction that convey increased risk for addiction. This finding identifies markers of vulnerability, as well as new targets for medications development, with the potential to personalize, and thereby improve, treatment based on patients' genetic profiles. Clinical trials are exploring new medications and behavioral therapies for tobacco addiction. A promising approach, which already completed Phase II clinical testing, is that of immunotherapy. A nicotine vaccine (NicVAX), which binds nicotine in the blood, preventing it from ever reaching the brain, showed strong positive results in promoting abstinence among study participants who achieved sufficient antibody levels. Further studies are helping to define optimal protocols for vaccination to improve results in all smokers. This may be a particularly useful tool for tobacco cessation programs in the not-too-distant future.

→ Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and productivity losses United States, 1997-2001. *Morb Mortal Wkly Rep* 2005;54:625-8.
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Institute of Medicine. *Ending the Tobacco Problem: A Blueprint for the Nation.* Washington, DC: National Academies Press; 2007.
→ For more information, see http://www.drugabuse.gov/ResearchReports/Nicotine/Nicotine.html
→ For more information, see http://cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDA**, NCI) (GPRA)

According to a Government Survey, 38 Percent of Adults and 12 Percent of Children Use Complementary and Alternative Medicine: In December 2008, NIH and the National Center for Health Statistics released new findings on Americans' use of complementary and alternative medicine (CAM). The findings are from the 2007 National Health Interview Survey (NHIS), an annual in-person survey of Americans regarding their health- and illness-related experiences.

According to the survey, approximately 38 percent of adults and nearly 12 percent of children use some form of CAM. For both adults and children, the most commonly used type of CAM is nonvitamin/nonmineral natural products, and the most common use for CAM is to treat pain. Although overall use of CAM among adults has remained relatively stable since 2002 (the last time NHIS included a CAM section), the use of some specific CAM therapies has varied substantially; for example, deep breathing, meditation, massage therapy, and yoga have all shown significant increases. The 2007 NHIS was the first to ask about CAM use by children. The NHIS also reports on characteristics of CAM users, such as gender, age, education, geographic region, poverty status, and health indicators. The 2007 NHIS provides the most current, comprehensive, and reliable source of information on Americans' use of CAM. These statistics confirm that CAM practices are a frequently used component of American's health care regimens, and reinforce the need for rigorous research to study the safety and effectiveness of these therapies. The data also point out the need for patients and health care providers to openly discuss CAM use to ensure safe and coordinated care. Future analyses of these data may help explain some of the observed variation in the use of individual CAM therapies and provide greater insights into CAM use patterns among Americans.

→ Barnes PM, et al. *Natl Health Stat Report* 2008;(12):1-23. PMID: 19361005.
→ For more information, see http://www.cdc.gov/nchs/data/nhsr/nhsr012.pdf
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NCCAM**, CDC)

Half of Surveyed Physicians Use Placebo Treatments for Patients: Treating patients with placebos has a long, complicated, and often controversial history. Nonetheless, little actually is known about U.S. physicians' current attitudes toward and use of placebo treatments. A national survey funded in part by NIH looked at placebo-prescribing practices among 679 internists and rheumatologists—specialties that commonly treat patients with debilitating chronic conditions. The survey found that about half of the physician respondents prescribed placebo treatments on a regular basis. Most (62%) said they think the practice is ethical. Among physicians who prescribed placebos, few said they used inert treatments such as saline injections or sugar pills; they were more likely to recommend over-the-counter analgesics (41%) or vitamins (38%), and some used antibiotics (13%) or sedatives (13%) as placebos. The survey also found that the physicians who used placebos rarely described them as such to patients. Instead, physicians most commonly described the treatments as medicine that typically is not used for the patient's condition but that might be beneficial. The survey provides insights into the complex relationship between placebo use and physicians' traditional role in promoting positive expectations in their patients. It also raises concerns about the use of "active" placebos, particularly antibiotics and sedatives, when they are not medically indicated. Prescribing placebo treatments remains an appropriate topic for ethical and policy debates.

→ Tilburt JC, et al. *BMJ* 2008 Oct 23;337:a1938. PMID: 18948346. PMCID: PMC2572204.
→ For more information, see http://nccam.nih.gov/research/results/spotlight/102408.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NCCAM**)

Research Resources, Infrastructure and Technology

Unique Compounds Added to Chemical Libraries: Potent, drug-like molecules that selectively bind to the kappa opioid receptor have potential utility in the treatment of drug addiction, depression, psychosis and dementia, pain, and even HIV infection. Well more than 100 unique, new molecules constructed independently by two NIH-supported groups have been found to provide entirely new classes of kappa opioid binders. These molecules are potent and display a diversity of pharmacological activities that are under intensive active investigation.

→ Beeler AB, et al. *J Comb Chem* 2005;7(5):673-81. PMID: 16153061.
→ For more information, see http://www.cmld.ku.edu/sbc_photos.shtml
→ For more information, see http://pdsp.med.unc.edu/indexR.html
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIGMS**) (GPRA)

National Centers for Biomedical Computing: There are seven NIH Roadmap National Centers for Biomedical Computing (NCBC). Funded as cooperative agreements, these centers collectively cover broad areas of neuroinformatics, functional genomics, image post processing, multiscale modeling, cellular pathways, semantic data integration and ontologies, information networks, cellular networks and pathways, clinical informatics, disease-gene-environment analysis, and clinical decisions support.

→ For more information, see http://ncbcs.org/
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Technology Development*
→ (E) (**NIGMS**, Common Fund - all ICs participate)

Influenza Virus Resources: NIH maintains the Influenza Virus Resource, a database of influenza virus sequences that enables researchers around the world to compare different virus strains, identify genetic factors that determine the virulence of virus strains, and look for new therapeutic, diagnostic, and vaccine targets. The resource was developed using publicly accessible data from laboratories worldwide in addition to targeted sequencing programs such as NIH's Influenza Genome Sequencing Project. Updated daily, this comprehensive sequence resource includes more than 90,000 influenza sequences and more than 2,000 complete genomes. In the spring of 2009, with the rapid emergence of the 2009 H1N1 pandemic, the database received more than 2,200 influenza sequences from publicly accessible databases and included sequences from CDC and labs from 35 countries. By the end of 2009, nearly 10,000 H1N1 sequences were in the database. The combination of extensive sequence data and advanced analytic tools provided researchers worldwide immediate access for investigating the rapid spread of this flu and developing vaccines for combating it. Other influenza virus information resources also were developed in response to 2009 H1N1. To facilitate access to the scientific literature, a pre-formulated search for 2009 H1N1 papers was added to PubMed. A 2009 H1N1 Flu page with comprehensive information on Federal response, international resources, transmission, prevention, treatment, genetic makeup, and veterinary resources was added to Enviro-Health Links, which provides links to toxicology and environmental health topics of recent special interest, including information in Spanish. For the general public, patients, family members, and caregivers, a health topic on 2009 H1N1 flu, in Spanish and English, was added to the MedlinePlus consumer health resource.

→ Bao Y, et al. *J Virol* 2008;82(2):596-601. PMID: 17942553. PMCID: PMC2224563.
→ For more information, see http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html
→ For more information, see http://www.pubmed.gov
→ For more information, see http://sis.nlm.nih.gov/enviro/swineflu.html
→ For more information, see http://www.nlm.nih.gov/medlineplus/h1n1fluswineflu.html
→ For more information, see http://www.nlm.nih.gov/medlineplus/spanish/h1n1fluswineflu.html
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**NLM**)

Centers of Excellence for Influenza Research and Surveillance: NIH established the Centers of Excellence for Influenza Research and Surveillance (CEIRS) program in March 2007 to continue and expand its animal influenza surveillance program internationally and domestically, and to focus on several high-priority areas in influenza research.

The program provides the government with information and public health tools and strategies to control and lessen the impact of epidemic influenza and the increasing threat of pandemic influenza. CEIRS activities lay the groundwork for the development of new and improved control measures for emerging and reemerging influenza viruses. Such measures include determining the prevalence of avian influenza viruses in animals in close contact with humans; understanding how influenza viruses evolve, adapt, and transmit; and identifying immunological factors that determine disease outcome. Each CEIRS site focuses on either (1) animal influenza surveillance for the rapid detection and characterization of influenza viruses with pandemic potential, or (2) pathogenesis and host response research to enhance understanding of the molecular, ecological, and/or environmental factors that influence pathogenesis, transmission, and evolution of influenza viruses; and to characterize the protective immune response. Currently, the CEIRS are responding to the 2009 H1N1 influenza outbreak by conducting research on pathogenicity and transmission of H1N1 and studying immune response to this novel influenza strain.

→ For more information, see http://www3.niaid.nih.gov/topics/Flu/default.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIAID**)

Collective Intelligence for Knowledge Discovery: NIH has started a new NIH initiative in collective intelligence. The goal is to create deep repositories of knowledge backed by controlled vocabularies or ontologies, and to create or enhance semantically interoperable applications capable of discovering knowledge hidden within these repositories. Current applications such as the Human Salivary Proteome Annotation System, the Common Assay Reporting System, and the caBIG Protocol Lifecycle Tracking Tool are among the initial steps of a knowledge infrastructure. These applications harvest the collective knowledge of targeted scientific communities to store protocols, data, and results. Other tools developed for this initiative (e.g., the context-sensitive text mining system for identification of high-risk, high-reward research) use statistical natural language processing to discover new knowledge, such as, whether in peer review, an application for funding was considered high-risk and high-reward. Additional pilot studies are evaluating computational linguistics and knowledge management tools for biomedical and clinical informatics, portfolio analysis, systems biology, proteomics, genomics, and knowledge representation paradigms. The collective-intelligence initiative will lead to a knowledge infrastructure that can shift the paradigms of data re-use and knowledge discovery dramatically.

→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**CIT**, CC, NCI, NHGRI, NIDCR, NIMH, OD)

NIGMS/NCI Collaborative Access Team (GM/CA-CAT): Structural biology is a field in which scientists learn about molecules by determining their 3-D structures in atom-by-atom detail. Large user facilities called synchrotrons allow researchers to use X-rays to determine molecular structures more easily, quickly, and cheaply than ever before. Two NIH institutes (NIGMS and NCI) funded the development of a new experimental station at the Advanced Photon Source at Argonne National Laboratory. The new station includes three X-ray beamlines for use by scientists from across the United States to determine the detailed, three-dimensional structures of molecules. Two of these beamlines provide world-leading capabilities for X-ray diffraction data from very small protein crystals only a few microns in dimension. This research capability is important to understand basic biological processes and for drug design. The facility now is in full operation.

→ For more information, see http://www.gmca.anl.gov
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIGMS**, NCI)

Collaborations Between Minority-Serving Institutions and Cancer Centers: The Minority Institution (MI)/Cancer Center (CC) Partnership (MI/CCP) is a flagship program that has been instrumental in establishing strong collaborations between minority-serving institutions (MSIs) and CCs. MI/CCP has fostered strong cancer research partnerships throughout the United States. This program established new cancer research curricula, recruited new faculty, increased awareness about health care disparities and cultural sensitivities, and developed programs and outreach efforts in educating underserved communities. The MI/CCP has provided research education and training to individuals at all levels including postdoctoral fellows, medical students, graduate students, students at master's level, and baccalaureate and high school students. Establishing new collaborations and partnerships in communities has been a hallmark of this program, culminating in increases in numbers of awarded grant applications and numbers of manuscripts, oral presentations, and poster presentations at both regional and national levels. Many research advances are emerging from the Partnership. For example, through the Morehouse School of Medicine and University of Alabama Partnership, researchers have identified a possible genetic cause for increased risk for a more advanced form of colorectal cancer in blacks that leads to shorter survival. Understanding the relationship between molecular defects and differences in colorectal cancer incidence, aggressiveness, and clinical outcomes is important in individualizing the treatment and in eliminating racial disparities.

→ For more information, see http://crchd.cancer.gov/research/miccp-overview.html
→ For more information, see http://clincancerres.aacrjournals.org/cgi/content/full/15/7/2406
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCI**)

Biomedical Technology Research Centers (BTRCs): The BTRCs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Centers and through intensive collaborations with other leading laboratories. The BTRCs are used annually by nearly 5,000 scientists from across the United States and beyond, representing more than $700 million of NIH funding from 22 ICs. As an example, optical technologies enable researchers to:

- Harness the power of light to "see" biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

→ For more information, see http://www.ncrr.nih.gov/biomedical_technology
→ This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
→ (E) (**NCRR**)

Extramural Construction Program Expands Research Capacity: The American Recovery and Reinvestment Act (ARRA) provided $1 billion to NIH for the Extramural Construction program. The program will build capacity to conduct biomedical and behavioral research by supporting the costs of improving non-Federal basic research, clinical research, and animal facilities to meet the research, research training, or research support needs of institutions. One component of the program, the Extramural Research Improvement Program, awards grants to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities for biomedical and behavioral research. Another component of the program, the Core Facility Renovation, Repair, and Improvement activity, awards

grants to public and nonprofit private entities to renovate, repair, or improve core facilities. A core facility is a centralized shared resource that provides access to instruments or technologies or services, as well as expert consultation to investigators supported by the core. Institutions apply for construction grants by submitting applications, which are selected using NIH's standard, competitive, peer-reviewed process. Funding decisions are based on the scientific and technical merit of the application as determined by first and second level of peer review, the availability of funds, the relevance of the application to NIH program priorities, the national geographic distribution of awards, and the priorities specified in the ARRA, such as energy efficiency and job creation. The objective of the ARRA Extramural Construction program aligns with the objective of the existing Research Facilities Improvement Program, which is also administered by NIH.

→ For more information, see http://www.ncrr.nih.gov/recovery/construction
→ This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
→ (E) (**NCRR**) (ARRA)

Shared Instrumentation Grant and High-End Instrumentation Programs: The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the $100,000-$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the $750,000-$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located at core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2008, the SIG program funded a total of 82 grants for $30,623,406; the HEI funded a total of 20 awards for $33,309,434. In FY 2009, NIH received $300 million in ARRA funding to provide shared instrumentation to extramural researchers through the SIG and HEI programs. To best serve the needs of NIH-supported investigators, the range of HEI awards funded by ARRA was expanded and now is $600,000 to $8 million.

→ For more information, see http://www.ncrr.nih.gov/btinstruments
→ For more information, see http://www.ncrr.nih.gov/recovery
→ This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
→ (E) (**NCRR**) (ARRA)

Stimulating Innovation

The NIH Director's New Innovator Award Program: The NIH Director's New Innovator Award addresses two important goals: stimulating highly innovative research and supporting promising new investigators. The award supports new investigators who propose exceptionally innovative research ideas but lack the preliminary data required to fare well in the traditional NIH peer review system. Award recipients have discovered important insights about Parkinson's genes and manganese poisoning, and protein folding and diabetes.

- *Link between Parkinson's disease genes and manganese poisoning:* Manganese poisoning, prevalent in such occupations as mining, welding, and steel manufacturing, damages the central nervous system, producing motor and dementia symptoms that resemble Parkinson's disease. One New Innovator recipient's team found a genetic interaction between two Parkinson's disease genes (alpha-synuclein and PARK9) and determined that the PARK9 protein can protect cells from manganese poisoning. Yeast cells contain a gene nearly identical to PARK9, and the team showed that expression of this gene protects yeast cells from the toxicity caused by alpha-synuclein. The team

found that the PARK9 gene in yeast also codes for a metal transporter protein. Cells with a defect in this gene, coupled with manganese exposure, did not grow well. These results may explain the origin of at least one type of Parkinson's disease.

- *Protein folding and diabetes:* Individual protein molecules do not always fold correctly into their normal shapes. A compartment within cells called the endoplasmic reticulum (ER) acts as a protein-folding factory for secreted proteins such as insulin. Another New Innovator recipient hypothesized that unrelenting insulin production can overtax the ER, leading to the condition of "ER stress." This triggers a chain of events that leads the insulin-making beta cells to commit suicide. This new knowledge could be used to identify new molecules as targets for the development of what may prove to be totally new types of drugs to fight diabetes.

  → Merksamer PI, et al. *Cell* 2008;135(5):933-47. Comment in *Cell* 2008;135(5):78-9. PMID: 19026441. PMCID: PMC2739138.
  → For more information, see http://www.nature.com/ng/journal/v41/n3/abs/ng.300.html
  → (E) (**NIGMS**)

The NIH Director's Pioneer Award: The NIH Director's Pioneer Award Program is designed to support highly innovative approaches to addressing major challenges in biomedical and behavioral research. By supporting scientists of exceptional creativity who propose pioneering and possibly transformative approaches, NIH intends to encourage novel investigator-initiated research that would have an unusually high scientific impact. Already, several recipients of the Award have discovered important insights, e.g., in Parkinson's disease, therapies for neurodegenerative diseases, and targets for cancer therapies.

- *Parkinson's disease and possible treatments:* Using an approach dubbed "optigenetics," one Pioneer Award recipient found that stimulating axons that connect directly to the subthalamic nucleus from areas closer to the surface of the brain in rodents has the biggest effect on treating "parkinsonism." This insight could lead to the development of less invasive treatments for patients with Parkinson's disease.
- *Personalized therapies for neurodegenerative diseases using RNA to reprogram cells*: Another recipient has shown that by flooding a nerve cell with a specific type of messenger RNA from another cell type, researchers could reprogram the nerve cell. The approach, called Transcriptome Induced Phenotype Remodeling, suggests a new type of cell-based therapy for neurodegenerative and other diseases.
- *Research in mice and human cells suggests new cancer therapeutic targets*: Another Pioneer Award study showed that a single extra copy of a particular gene on chromosome 21 is sufficient to significantly suppress angiogenesis (growth of new blood vessels) and tumor growth in mice, as well as angiogenesis in human cells. The study also showed that the protein expressed by the gene under study, DSCR1, is elevated in tissues from people with Down syndrome and in a mouse model of the disease. Given that the incidence of many cancers is significantly reduced in individuals with Down syndrome, this finding suggests a new target for cancer therapies.

  → Gradinaru V, et al. *Science* 2009:324(5925):354-359. PMID: 19299587.
  Sul JY, et al. *Proc Natl Acad Sci U S A* 2009;106(18):7624-9. PMID: 19380745. PMCID: PMC2670883.
  → For more information, see http://www.nature.com/nature/journal/vaop/ncurrent/full/nature08062.html
  → (E) (**NIGMS**)

Building Interdisciplinary Research Teams (BIRT) Awards: The scale and complexity of biomedical research demands that scientists move beyond the confines of their individual disciplines and explore new organizational models for team science. Integrating different disciplines holds the promise of opening scientific avenues of inquiry and, in the process, potentially forms new disciplines for addressing increasingly complex questions. The BIRT award was created by NIH to promote interdisciplinary research by supplementing collaborations with high innovation and potentially high impact in general areas of arthritis, musculoskeletal, and skin biology and diseases. In 2008, 11 grants were awarded for

the following areas of collaboration: developmental biology—systems biology, soft tissue biology—imaging technologies, tissue engineering—immunology, and tissue engineering—developmental biology.

→ For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2008/birt.asp
→ For more information, see http://www.niams.nih.gov/Funding/Funding_Opportunities/Supported_Scientific_Areas/Musculoskeletal_Diseases/birt_faq.asp
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-08-001.html
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIAMS**)

Cancer Health Disparities Research Programs and Initiatives: NIH has expanded research on the basic biologic factors of cancer disparities to provide a foundation for minimizing risk, identifying targets, developing preventive and therapeutic interventions, and understanding how genetic susceptibility may be influenced by social, economic, race/ethnicity, and geographic factors. Thus, the research programs involve multidisciplinary teams, which contribute to understanding the etiology of cancer and build prevention and intervention evidence-based models to eliminate cancer disparities. Several programs at NIH address disparities along the cancer continuum from prevention to survival.

- The trans-disciplinary Geographic Management Program (GMaP) pilot initiative builds regional networks to support research, training, and infrastructure to develop state-of-the-art networks/centers to ensure a continuous supply of high-quality human biospecimens from multi-ethnic communities.
- The Community Networks Program engages communities experiencing cancer disparities to design, test, and evaluate evidence-based strategies to address critical needs, such as access to screening, mentoring, and training; policy development; and community outreach and education.
- The Patient Navigation Research Program builds partnerships to ensure that racial/ethnic minorities and underserved populations with abnormal cancer screening results receive appropriate care.
- The Community Clinical Oncology Program is a network for conducting cancer prevention and treatment clinical trials by connecting academic centers with community physicians.
- The NIH Centers for Population Health and Health Disparities catalyze transdisciplinary research to improve the understanding of complex interactions of biological, social, cultural, environmental, and behavioral factors that contribute to health inequities, and to develop and implement novel intervention strategies that are multilevel and multifactorial.
- The Tobacco Research Network on Disparities' mission is to understand and address tobacco-related disparities by advancing the science, translating that scientific knowledge into practice, and informing public policy.
- The Centers of Excellence in Cancer Communication Research continue to use best practices in communication science to extend the reach of biomedical benefits equitably throughout the population.

→ For more information, see http://crchd.cancer.gov/
→ For more information, see http://crchd.cancer.gov/cnp/background.html
→ For more information, see http://crchd.cancer.gov/pnp/pnrp-index.html
→ For more information, see http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCI**)

Cooperation in Space-Related Health Research: In FY 2009, NIH and the National Aeronautics and Space Administration (NASA) issued a funding opportunity announcement to support biomedical experiments that astronauts could perform on the International Space Station (ISS). The ISS provides a special microgravity and radiological environment that Earth-based laboratories cannot replicate. Congress, recognizing the immense promise the facility holds for American-led science and technology efforts, opened the U.S. portion of the ISS to other Federal agencies and

university and private sector researchers when it designated the U.S. resources as a National Laboratory in 2005. Recently published ISS experiments from investigators supported by NIH and NASA have offered new insights into how bacteria cause infectious disease. The FY 2009 solicitation is the next step in a partnership to apply the National Laboratory to research that complements NASA's space exploration efforts. The program encourages a new cadre of health researchers from a variety of disciplines to incorporate the space environment into their experiments, and will support them as they prepare their experiments for launch and analyze their data following a mission. Applications particularly are encouraged from researchers who are interested in molecular or cellular biology, biomaterials, or telemedicine. NIH expects to fund applications in FY 2010, FY 2011, and FY 2012, and to send experiments into space by 2011.

→ Wilson JW, et al. *Proc Natl Acad Sci U S A* 2007;104(41):16299-304. PMID: 17901201. PMCID: PMC2042201.
→ For more information, see http://www.niams.nih.gov/News_and_Events/NIH_NASA_Activities/default.asp
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIAMS**, NCI, NCRR, NHLBI, NIA, NIAAA, NIBIB, NICHD, NINDS)

[31] Liu GY, et al. *J Exp Med* 2005:202(2):209-15. PMID: 16009720. PMCID: PMC2213009.
[32] For more information, see http://www.nih.gov/news/health/feb2008/nigms-14.htm.
[33] Liu CI, et al. *Science* 2008;319(5868):1391-4. PMID: 18276850. PMCID: PMC2747771.
[34] Song Y, et al. *J Med Chem* 2009:52:3869-80. PMID: 19456099. PMCID: PMC2753857.
[35] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-040.html.
[36] Ganeshan K, et al. *J Allergy Clin Immunol* 2009;123(1):231-238.e4. PMID: 19022495. PMCID: PMC2787105.
[37] Kawasaki Y, et al. *Nat Med* 2008;14:331-6. PMID: 18264108. PMCID: PMC2279180.
[38] Li J, Wang C-Y. *Nat Cell Biol* 2008;10(2):160-9. PMID: 18193033.
[39] Nesti LJ, et al. *J Bone Joint Surg Am* 2008;90(11):2390-8. PMID: 18978407. PMCID: PMC2657299.
[40] Gowher H, et al. *Genes Dev* 2008;22:2075-84. PMID: 18676812. PMCID: PMC2492749.
[41] For more information, see http://nihroadmap.nih.gov/epigenomics/fundedresearch.asp.
[42] Denny P, et al. *J Proteome Res* 2008;7(5):1994-2006. PMID: 18361515. PMCID: PMC2839126.
[43] For more information, see http://www.nih.gov/news/research_matters/february2009/02232009cancer.htm.
[44] Shukla AK, et al. *Mol Pharmacol* 2008;73(5):1333-8. PMID: 18239031.
[45] Rasmussen SG, et al. *Nature* 2007;450:383-7. PMID: 17952055.
[46] Service RF. *Science* 2009;325(5945):1200. PMID: 19729635.
[47] Mazumdar V, et al. *J Bacteriol* 2008;191(1):74-90. PMID: 18931137. PMCID: PMC2612419.

Clinical and Translational Research

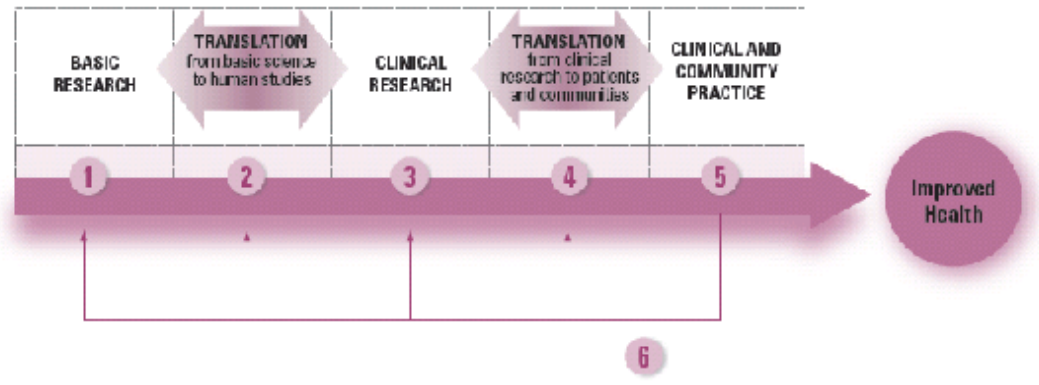
The obesity epidemic combined with an aging population has made diabetes the most common cause of kidney failure, nontraumatic lower limb amputation, and new cases of blindness among working-age Americans. Diabetes also is a leading cause of heart disease and stroke. Nearly 11 percent of American adults 20 years and older have diabetes and 57 million have pre-diabetes—elevated blood sugar levels not yet in the diabetic range. African Americans, Hispanic/Latino Americans, American Indians, Asian Americans, and Pacific Islanders are at particularly high risk.[48] Globally, more than 180 million people have diabetes, and the number is likely to more than double by 2030.[49]

The landmark NIH-supported Diabetes Prevention Program (DPP) clinical trial sought ways to prevent type 2 diabetes and found that a lifestyle intervention—reduced dietary fat and calories, moderate exercise, and a goal of a 7 percent reduction in body weight—lowered the risk of developing type 2 diabetes by 58 percent. Study participants receiving the drug metformin along with standard medical advice about diet and exercise had a 31 percent lower risk than those receiving standard medical advice alone. The interventions worked in all ethnic and racial groups studied, in both men and women, and in women with a history of gestational diabetes,[50,51] The DPP Outcomes Study continues to follow most of the participants to evaluate the lasting benefits of the interventions. The critical challenge today is to move this proven program into widespread use. NIH is supporting translational research to find better methods for identifying people with pre-diabetes and to develop cost-effective ways of implementing the DPP-based lifestyle intervention. One successful program is delivering a lifestyle intervention based on the DPP in a group setting at YMCAs.[52]

Introduction

As the steward of medical and behavioral research for the Nation, NIH is supporting scientific research in pursuit of fundamental knowledge about the nature and behavior of living systems and the mechanisms of disease. Achieving this mission requires a research continuum from basic discovery to accelerated translation of biomedical discoveries into clinical and community practice, with feedback loops at every step (Figure 3-1). In this report, clinical and translational research are considered together because the two areas overlap, with translational efforts often focusing on dismantling barriers that slow the progress of clinical research or impede the adoption of new and effective interventions.

Figure 3-1. NIH Supports the Full Continuum of Biomedical Research



1. The research continuum begins with **basic research**—the study of the fundamental mechanisms of disease and behavior. Basic research is a major force for progress in the biomedical and behavioral sciences and can lead to insights essential to understanding basic human biology and behavior in both normal and diseased states. Basic research is thus a

critical component of the Nation's public investment in research and a central feature of NIH's research program. (Also see the section on *Molecular Biology and Basic Sciences* in Chapter 3.)

2. NIH is a key supporter of **early (or preclinical) translational research**—studies that serve as a bridge between basic science and human medicine. The early translational stage applies fundamental laboratory discoveries to the preclinical development of studies in humans. Such early translational investigations often are carried out using animal models, cultures, samples of human or animal cells, or a variety of experimental systems such as computer-assisted modeling of disease progression and drug therapy.

3. **Clinical research** is patient-oriented research that is conducted with human subjects (that is, studies that involve direct interaction between investigators and human subjects or the use of material of human origin, such as tissues, specimens, and data that retain information that would allow the investigator to readily ascertain the identity of the subject). Clinical research includes clinical trials, behavioral and observational studies (also see the section on *Epidemiological and Longitudinal Studies* in Chapter 3), outcomes and health services research, as well as the testing and refinement of new technologies. Investigations that use only anonymous specimens or other "de-identified" data from human subjects, however, are excluded from the umbrella of clinical research. Such studies would likely fall into the categories of basic or early translational research.

Clinical trials, a crucial subset of clinical research, are the best method of determining whether interventions are safe and effective in people and assessing side effects or other complications. Trials are designed to answer specific research questions about a biomedical or behavioral intervention. For example, treatment trials might test experimental drugs or devices, new combinations of drugs, innovative approaches to surgery or radiation therapy, or behavioral interventions such as exercise training or medication adherence. Prevention trials test the effectiveness of approaches to prevent diseases or other adverse health conditions or to keep them from recurring. Comparative effectiveness research entails real-world comparisons of known interventions. (Also see the section on *Chronic Diseases and Organ Systems* in Chapter 2.) Screening and diagnostic trials are conducted to find better ways to detect or diagnose diseases or conditions. Finally, quality-of-life trials (or supportive care trials) explore ways to improve people's comfort and ability to continue the activities of daily life even as they deal with chronic illnesses or approach the end of life.

NIH also funds the development of consortia, cooperative study groups, and networks that enable a single institution or researcher to combine resources and knowledge with others. Consortia are particularly useful for studying rare diseases, and they allow clinical trials to more rapidly recruit sufficient numbers of participants to speed the delivery of new treatments to patients. The matrix of research support arising from such partnerships creates a whole that is much greater than the sum of the separate programs.

4. A key goal of NIH research efforts is to bring effective prevention and treatment strategies more quickly into practice to improve population health, both domestically and globally. The **late (or postclinical) translational stage** takes results from studies in humans and applies them to research on enhancing the adoption of best practices in the community. NIH investigates strategies for disseminating information to providers and the public about the latest research findings and encourages health care providers to participate in clinical research.

NIH collaborative activities in translational research take place within most ICs and almost every other HHS agency. The collaborations include working groups and committees such as the Biomedical Imaging in Oncology Forum, the Joint Working Group on Telehealth, and the Health Literacy Workgroup; a wide range of translational research such as projects on vaccine safety, child abuse and neglect, diabetes prevention, and health disparities; and database development and management such as the Stem Cell Therapeutics Outcomes Database.

The Federal government plays a critical role in focusing on gaps in clinical and translational research that would otherwise remain unaddressed by other entities (e.g., pharmaceutical companies, nonprofit organizations). Specifically, NIH supports clinical and translational studies unlikely to garner substantial investment by other sources because of insufficient financial

incentives—for example, studies that address rare diseases, are considered high risk, or are based on lifestyle alterations or behavioral changes rather than drugs or devices.

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5. Important new discoveries can improve population health and reduce disease burdens only if they are integrated into care. Therefore, NIH is taking a lead in applying evidence-based methods to inform the public and health care practitioners about research results and facilitate the implementation of safe and effective interventions in the **community and the clinic**.

6. Although sometimes referred to as bench-to-bedside research, translational research is really a two-way street, with each stage informing and influencing the others. Basic research scientists provide clinicians with new tools for use with patients, and clinical researchers make new observations about the nature and progression of disease that often feed back to stimulate new basic investigations. Research on new outreach approaches and the comparative effectiveness of prevention and treatment strategies also are important activities to ensure the feasibility of such strategies and to inform the development of future interventions.

Every NIH component supports clinical and translational research. NIH's ICs oversee a broad portfolio of clinical and translational research that encompasses intramural and extramural programs. (Also see the section on *Extramural and Intramural Research Programs* in Chapter 1.) NIH intramural research laboratories are conducting cutting-edge biomedical research in a wide range of fields at its main campus in Bethesda, Maryland, and several satellite locations. Central to the intramural program is the NIH Clinical Center, the Nation's largest hospital devoted entirely to clinical research. The Clinical Center serves more than 7,000 inpatients and more than 100,000 outpatients annually. To receive medical care at the Clinical Center, individuals need to meet the eligibility criteria for and agree to participate in a research trial.

The NIH extramural program, in addition to supporting both investigator- and NIH-initiated clinical and translational research, builds collaborations among institutions, industry (e.g., pharmaceutical companies), and local communities; sets up innovative centers of clinical and translational research; undertakes animal and other preclinical studies; and develops new resources and tools for research. Training and career development initiatives help ensure that enough highly trained and diverse groups of basic, clinical, and translational scientists are available with appropriate research knowledge to carry out the country's biomedical and behavioral research agendas. (Also see the section on *Research Training and Career Development* in Chapter 3.)

NIH Roadmap initiatives are helping to accelerate and strengthen movement along the research continuum by ensuring that basic discoveries are translated into interventions to improve health. These initiatives are supporting the development of research networks, outcome assessment tools, core services and resources, policy enhancement and harmonization, and a Clinical and Translational Science Award (CTSA) program. Thanks to such programs, the clinical research enterprise is being transformed to speed the progression of new discoveries from bench to bedside and community.

Catalogs of Clinical and Translational Research Activities

In response to the mandate under SEC. 403 (a)(4)(C)(v) of the Public Health Service Act to provide a catalog of clinical trials, provided here is a live link to the service called ClinicalTrials.gov, a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov provides information about a trial's purpose, who may participate, locations, and phone numbers for more details.

In response to the mandate under SEC. 403 (a)(4)(C)(v) of the Public Health Service Act to provide a breakdown of study populations by demographic variable, provided here is a link to NIH's Biennial Report on its tracking efforts regarding study demographics: *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*. (Please also see Appendix D, which provides an excerpt of that report.)

In response to the mandate under SEC. 403 (a)(4)(C)(vi) for a catalog of translational research activities with other agencies of the Public Health Service, included here is a live link to the Catalog of Trans-HHS Translational Research Activities FYs 2007 & 2008. This is an excerpt from another congressionally mandated report, the Annual Report to the Secretary, HHS, on *NIH Collaboration with Other HHS Agencies.*

Summary of NIH Activities

NIH nurtures strategies that bring basic research discoveries to human studies, optimize the conduct of clinical research, and facilitate the transfer of new knowledge gained through research into clinical practice, thereby aligning and reinforcing the entire research continuum. The following summary delineates some specific strategies employed by the ICs to propel research along the research continuum and highlight a few examples from NIH's robust portfolio of clinical and translational research.

Preclinical Research: Translating Basic Science Discoveries to Human Studies

Before investigators can conduct human studies, extensive basic and preclinical research must be done and a supportive infrastructure must be in place. NIH equips translational scientists with research tools, enhances opportunities for collaborative research, and provides resources for developing and testing new drugs before progressing to human studies. The result has been the creation of exciting possibilities in terms of new investigational drugs and devices ready for safety and efficacy testing in humans, including:

- In the past 2 years, NIH-funded scientists have published several papers on compounds that improve muscle function and endurance in animals. They hope that this new knowledge can be applied to improve treatments for certain muscle disorders, frailty, obesity, and other conditions.
- Laboratories have been established to screen promising compounds for treating alcohol dependence in animal models, thereby enabling faster determination of those that merit advancement to large, multisite studies.
- NIH-supported investigations have successfully decoded the genome of the parasite that causes relapsing malaria and determined that the anti-malarial drug chloroquine may once again be used to prevent malaria in African children.

Research Tools and Resources

Preclinical research results derived from animal models are an essential element in the translational process of determining whether a basic science discovery is a potential therapeutic approach worthy of future development. Scientists who work with animal models can look forward to a new online tool to increase research efficiency, improve collaboration, and ultimately help bridge the gap between basic science and human medicine. With funding from NIH, the Linking Animal Models to Human Disease Initiative will integrate data and information about animal models and make them available to health researchers to help them identify the most useful animal models for their research.

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Nonhuman primates are critical resources for translational research because of their close physiological similarities to humans. The NIH-supported National Primate Research Centers (NPRCs) and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using nonhuman primates. In FY 2008, more than 2,000 investigators used nonhuman primates from the NPRCs. One highlight

of research conducted at a NPRC was the development and characterization of the first nonhuman primate model of a neurodegenerative condition—Huntington's disease.[53] This new model will make it possible to study a wide range of therapeutic strategies to help people who have the devastating fatal disease.

Among the many research tools that NIH provides to promote early translational studies are biosample and data repositories. Central repositories allow additional studies on human tissue samples and data collected during clinical research, enhancing the value of each study and making optimal use of samples and data. The use of repositories also ensures that samples are stored under uniform conditions and are readily accessible to the scientific community. Samples and data are labeled with codes to keep the study participants' information confidential. Although numerous regulations and policies apply to research on human samples and data, currently no comprehensive Federal policy covers the full spectrum of activities involved with collection, storage, sharing, distribution, and use of human specimens or data for research. To address this gap, NIH is developing draft guidelines for human specimen and data collections owned or supported by NIH. The guidelines cover ethical and regulatory issues and provide vital information about managing, accessing, sharing, and using the stored specimens and data. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.)

A recent Alzheimer's Disease Neuroimaging Initiative study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer's disease and established a method and standard for testing for these biomarkers.

Researchers from several ICs are identifying, developing, and validating new biomarkers—physical, functional, or biochemical indicators of physiologic or disease processes. Biomarkers play important roles in the diagnosis of disease, identification of patient populations that could benefit from particular therapies, and the monitoring of treatment effectiveness. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a noteworthy example of an innovative public-private partnership for examining the utility of magnetic resonance imaging, positron emission tomography, or other methods to identify biomarkers that will enable clinicians and investigators to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease. ADNI has provided evidence to support development of a number of tools and methods now in use in the United States and abroad. A recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer's disease and established a method and standard for testing for these biomarkers. (Also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2 and the section on *Alzheimer's Disease Centers* in Chapter 4.)

Collaborative Science

Oftentimes, translational research can be streamlined or conducted more economically when scientists within NIH, private industry, academia, private practices, or other institutions work in partnership to complement each other's strengths and share costly resources or infrastructure. As its name implies, the NIH Bench-to-Bedside Program spans the research continuum with its focus on collaboration between basic and clinical investigators working to translate fundamental scientific discoveries into diagnostic and therapeutic applications at the bedside. This program also bridges the intramural and extramural research communities and fosters interagency collaborations.

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In addition, through the Strategic Partnering to Evaluate Cancer Signatures initiative, NIH is bringing together interdisciplinary teams at various institutions to discover, develop, and test biomarkers that can be used to characterize an individual's disease or tumor. Armed with such information, clinicians can tailor a patient's cancer treatment based on

molecular characteristics of the patient and tumor. Several published studies have already demonstrated the usefulness of this personalized approach to cancer therapy. (Also see the section on *Cancer* in Chapter 2.)

Resources for Developing and Testing Investigational Drugs

NIH helps bridge the gap between drug discovery and clinical testing of promising new agents. Translating promising compounds into drugs for human use is a task that requires very specific, interrelated activities. NIH provides state-of-the-science preclinical drug development resources. Specifically, NIH helps investigators by providing large quantities of promising investigational drugs to test in clinical trials, and clarifying regulatory issues so that FDA requirements are likely to be satisfied when the new investigational drugs are ready for testing in the clinic. For example, the NCI Experimental Therapeutics program (NExT) is an integrated drug discovery and development effort that concentrates research into a single robust pipeline that starts with discovery of promising compounds and follows a series of progressive steps leading to early-phase clinical studies. The NExT program aims to produce a diverse portfolio of assays and imaging tools that are available in the public domain. It is anticipated that this investment will reap many benefits by making a library of new molecular tools available to all researchers in the cancer research community for use in assessing new targeted drugs and diagnostics. (Also see the section on *Cancer* in Chapter 2.)

A menu of preclinical drug development contract resources is offered through one of NIH's Roadmap initiatives, the Rapid Access to Intervention Development (RAID) program. The NIH-RAID program makes accessible, on a competitive basis and at no cost to investigators, certain critical resources needed to develop new therapeutic agents, including not only laboratory services but also expertise in the regulatory process. The program directly addresses roadblocks to moving research findings from bench to bedside. Among the projects approved are potential therapies for hepatic fibrosis, sickle cell anemia, drug abuse, and Crohn's disease.

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To move basic research on Alzheimer's disease and associated disorders into the realm of translational research and drug testing in clinical trials, NIH is providing resources for preclinical development of investigational drugs and toxicology studies for academic and small business investigators who lack the resources to perform the required evaluations of promising therapeutic compounds. Several compounds already are undergoing testing, including anti-hypertensive drugs, anti-inflammatory drugs, and novel small molecules. (Also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2.)

Similarly, NIH has developed several focused translational research initiatives over the last decade in the area of neurological disorders. The Spinal Muscular Atrophy (SMA) Project, for example, is an innovative pilot program to develop a treatment for spinal muscular atrophy using a "virtual pharma" strategy that engages resources to carry out a drug development plan via contracts and collaboration. The project has two patents on compounds that show promise and is evaluating the safety of the most promising drug candidates, with the goal of a human clinical trial beginning in 2010. (Also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2.)

Clinical Research: Learning Which Interventions Work

Clinical research helps scientists develop and test interventions and new treatments. There are many types of clinical research. For example, some observational clinical research studies involve following a group of patients with a condition and determining their symptoms and responses to treatment in order to refine medical practice. Some studies help researchers and clinicians determine whether dosing schedules, behavioral changes, and other elements of a treatment plan are realistic and appropriate. Clinical research sometimes overlaps with the category of epidemiological studies, which is

described earlier in this chapter. These studies can help researchers develop new interventions that can be evaluated later in clinical trials.

Generally, clinical trials, particularly those evaluating drugs or medical devices, are conducted in phases, each of which helps scientists answer different questions. In a Phase I trial, researchers test an experimental drug or treatment in a small number of people (20-80) to evaluate its safety, determine a safe dosage range, and identify side effects. Phase II trials involve larger numbers of people (100-300) and evaluate the safety and effectiveness of the study drug or treatment. In Phase III trials, the experimental study drug or treatment is given to large numbers of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely. Phase IV, or postmarketing, studies are conducted to gather information associated with long-term use in various populations.

The randomized clinical trial has long been considered the gold standard for evaluating the effectiveness of investigational treatments. "Randomization" means that subjects are assigned by chance to either the investigational intervention or the control group. The control group might include interventions such as usual care; best proven care, if known; no treatment; or placebo. The specific clinical trial design is dependent upon the research questions posed. In addition to the use of control groups, clinical trials often use "blinded" or "masked" study designs, in which patient participants are purposely not told whether they are in the intervention or the control group. If feasible, clinical trials are often "double-blinded" or "double-masked," meaning that neither researchers nor participants know which people receive the intervention to ensure that the study results are unbiased.

Participation in clinical trials gives people an opportunity to contribute to the research effort and potentially gain early access to experimental treatments that might prove effective. For some participants, a study can provide expert medical care at a leading health care facility. Research risks and potential benefits are carefully balanced, and the burdens and benefits of participating are shared equally by appropriately including both sexes and people of all races/ethnicities and ages (see Appendix D). Balanced inclusion in trials allows investigators to know whether an intervention works equally well in different populations. NIH supports outreach efforts to recruit and retain children, women, and minorities in clinical studies. In addition, NIH recognizes the importance of developing sound scientific bases for pediatric care while protecting children adequately in research settings. NIH policy, therefore, requires that children (i.e., individuals younger than 21 years of age) be included in human subjects research conducted or supported by NIH, unless there are sound scientific or ethical reasons for excluding them. To help people access information about clinical trials for which they may be eligible, the ClinicalTrials.gov website offers general information about clinical trials and provides a searchable database of specific studies around the world.[54]

NIH recognizes that the involvement of human beings as participants in research creates ethical and regulatory responsibilities for the investigators and institutions conducting such research. NIH clinical research encompasses the principles of respect for persons, beneficence, and justice. Most clinical research is federally regulated with built-in safeguards to protect the participants. NIH, therefore, has established a system of research, review, approval, and oversight to assist investigators in understanding ethical principles and complying with regulatory requirements to maximize safety for research subjects. The informed consent process is carefully designed to ensure that study participants understand the risks and possible benefits of the research. Various NIH initiatives and programs seek to harmonize regulatory aspects governing the conduct of clinical research to ensure that studies are conducted with scientific rigor, with minimal burdens on research subjects and investigators, and with utmost consideration for the safety, rights, and welfare of subjects. (See also *Ensuring Responsible Research* in Chapter 1.)

Fostering Collaborative NIH Clinical Research

NIH support and activities along the research continuum are enriching the pipeline of biomedical discoveries. NIH funnels the majority of its funding for clinical trials to its extramural partners, which operate at the regional, State, and local levels. Studies often are conducted at multiple institutions. Such multisite clinical trials help investigators quickly recruit enough

subjects for studies; give the public the widest possible access to clinical studies; and address the special health concerns of high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. To test investigational therapeutic and preventive strategies in the most expeditious way and hasten their entry into the clinic, NIH is supporting a wide variety of collaborations, research centers, and networks to conduct efficient multicenter clinical trials.

To investigate effective treatments for mental disorders, NIH uses its extensive clinical trials networks as platforms for research. The networks, which are maintained through infrastructure supported by NIH, evolved from a recent series of practical clinical trials. The networks comprise more than 60 sites throughout the United States that maintain continual outreach efforts to diverse groups of patients and families with mental illnesses. The Depression Trials Network, for example, is seeking participants for the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. This study will examine for the first time whether two different depression medications, when given in combination as the first treatment step, compared to one medication, will enhance remission rates, increase speed of remission, be tolerable to the participant, and provide better sustained benefits in the longer term.

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NIH equips networks of investigators with the tools they need for successful collaboration and information sharing. NIH supports many clinical research networks by funding ongoing infrastructure that provides means of standardizing data reporting to enable seamless data and sample sharing across studies. Through NIH-funded informatics and other technologies, researchers are better able to broaden the scope of their research and avoid duplicating research efforts, thereby freeing time and funds to address additional research questions.

Among the numerous networks established by NIH that have generated significant findings are the Maternal and Fetal Medicine Units Network, Neonatal Research Network, Obstetric Pharmacology Research Network, Collaborative Pediatric Critical Care Research Network, Pelvic Floor Disorders Network, Traumatic Brain Injury Clinical Trials Network, the Alzheimer's Disease Cooperative Study, and the Global Network for Women's and Children's Health Research. Additionally, the NCI Community Cancer Centers Program is encouraging more patient and physician involvement in NIH-sponsored cancer trials, establishing new methods for tracking minority accrual, and improving specimen collection. NIH recently has initiated several additional networks, including the notable examples of the Hepatitis B Clinical Research Network and the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network. These new networks are expected to generate significant findings in the future.

Addressing Gaps in Research

In terms of clinical evaluation of drugs, there is no clear line where NIH-supported work stops and the pharmaceutical industry picks up. Every drug candidate presents its own profile of benefit and potential for gains in public health as well as financial risk. NIH's aim is to be sure that all important leads are followed until they are mature enough to attract private-sector interest or until they reach a dead end. About half of the chemotherapeutic drugs currently used by oncologists for cancer treatment were discovered and/or developed by NIH. Cisplatin for treating testicular, ovarian, and lung cancer; paclitaxel (Taxol) for treating several different cancers; and fludarabine phosphate for treating lymphoma are examples of how NIH involvement in early-stage drug development led to products that were licensed to commercial organizations and reached the market. In addition, NIH involvement has been central in developing effective interventions for diagnosis, management, or monitoring of HIV/AIDS, tuberculosis, arthritis, malaria, and many other conditions.

Government-funded research is particularly vital for the study of rare diseases. Not only do affected individuals benefit from new treatments that industry does not have the incentive to bring to market, but insights gained from such research often provide knowledge relevant to understanding more common diseases. For these reasons, NIH-funded investigators are studying an inherited retinal degenerative disease called Leber's congenital amaurosis (LCA), which causes severe vision loss in infancy or early childhood. NIH intramural scientists discovered that the *RPE65* gene plays a key role in the visual cycle—the set of biochemical interactions that converts light into an electrical signal to initiate vision. Mutations in this gene disrupt the visual cycle, resulting in LCA and blindness. As described in reports published in 2008 and 2009, an NIH-supported Phase I clinical trial of *RPE65* gene transfer in LCA found the treatment is safe and that visual function improved. Additional studies are exploring the range of therapeutic doses in adult and adolescent patients as well as rigorous evaluation of the effectiveness of this treatment. This clinical research is an important step in treating LCA and in establishing proof-of-concept for gene transfer as a therapy for eye disease.

Because behavioral interventions generally do not involve marketable products or services, NIH has a special role to play in research on how changes in behavior can improve health. For example, the Look AHEAD (Action for Health in Diabetes) study is examining the long-term health effects of an intensive lifestyle intervention (ILI) designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity. The study enrolled more than 5,100 overweight or obese adults with type 2 diabetes. Participants in the ILI group achieved clinically significant weight loss in the first year of the study; this was the case across all subgroups of the ethnically and demographically diverse study population. In addition, this weight loss was associated with an increase in health-related quality of life and improved cardiovascular fitness, blood pressure, cholesterol, and blood glucose levels, as compared to a control group receiving standard diabetes support and education. Look AHEAD seeks to determine whether the ILI reduces the incidence of heart attack and stroke, the leading causes of death among people with type 2 diabetes. This multicenter, randomized clinical trial involves several ICs as well as the Centers for Disease Control and Prevention.

The Look AHEAD (Action for Health in Diabetes) study is examining the long-term health effects of an intensive lifestyle intervention designed to achieve and maintain weight loss in overweight or obese people with type 2 diabetes through decreased caloric intake and increased physical activity.

One area where human research data often are lacking is the study of environmental effects on human health. Scientists working at the new Clinical Research Unit located on the NIH campus in Research Triangle Park, North Carolina, aim to narrow the gap between research and health care. The mission of the Clinical Research Unit is to translate basic laboratory findings to human studies; investigate interactions between genetic susceptibility and environmental factors in complex human traits and diseases; identify populations at risk; and develop novel preventive and therapeutic strategies to combat human diseases. Scientists who use the new facility are embarking on a diverse array of research studies involving pulmonary diseases, medical genetics, cardiovascular diseases, and reproductive health. The Clinical Research Unit also will provide advanced training opportunities for students and postdoctoral fellows whose research interests require access to clinical samples and patients.

Bariatric surgery is sometimes used in clinical practice as a treatment for severely obese adolescents despite a lack of evidence demonstrating its benefits for this population. NIH is addressing this research gap by supporting an observational study of teens already scheduled for surgery, Teen-LABS (Longitudinal Assessment of Bariatric Surgery). The Teen-LABS study is built upon the framework of the LABS consortium a group of surgeons, physicians, and scientists studying adult bariatric surgical outcomes. The Teen-LABS study will help determine whether bariatric surgery is an appropriate treatment option for extremely obese adolescents.

In response to another knowledge gap, NIH has launched the Clarification of Optimal Anticoagulation through Genetics (COAG) trial to gain a better understanding of the influences of clinical and genetic characteristics of patients in determining a safe and optimal dose of the drug warfarin, the most commonly used oral anticoagulant in the United States.

This prospective, multicenter, randomized clinical trial will recruit more than 1,200 patients who are beginning treatment with warfarin. The COAG study will help determine whether knowledge of some specific genes will help physicians find the safest, most effective warfarin dose for their patients. The drug is used to prevent dangerous blood clots that can potentially lead to pulmonary emboli and strokes, but the ideal dosage varies widely from one person to another. Getting the wrong amount of warfarin can be dangerous: If the dose is too high, patients could bleed profusely; if too low, life-threatening clots could develop. The knowledge gained in COAG will make significant scientific contributions to several medical specialties and help advance the field of personalized medicine.

Given the absence of a substantial commercial market, regulatory hurdles, and extensive clinical trial requirements, the private sector has little incentive to invest in biodefense measures. Biological weapons in the possession of hostile states or terrorists, as well as naturally occurring emerging and reemerging infectious diseases, are among the greatest security challenges to the United States. NIH, therefore, is fostering unique partnerships among government, industry, small businesses, and academia to facilitate the movement of promising products through all stages of the drug research and development pipeline, with the goal of developing vaccines and therapeutics against such biological threats as smallpox; botulism; Ebola, Marburg, and West Nile virus; avian influenza; and plague. (Also see the section on *Infectious Diseases and Biodefense* in Chapter 2.)

Putting Clinical Research Results into Practice

Throughout this report are descriptions of important studies that are changing the way health care is practiced in this country, improving public health and enhancing well-being. To fully realize the potential of new interventions, research results must be disseminated and put into widespread use. NIH carries out comparative effectiveness research (CER), investigates strategies for adoption of new evidence at the community level, trains health care providers in research skills, disseminates information to providers and the public based on the latest research findings, and sponsors research to learn about the most effective ways to disseminate such findings.

Comparing the Effectiveness of Different Therapies or Strategies

CER is the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in real-world settings. The purpose of such research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers about which interventions are most effective for which patients under specific circumstances. To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations and sub-groups. Defined interventions compared may include medications, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, and delivery system strategies. This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness and actively disseminate the results.[55]

In efficacy research, such as a drug trial for FDA approval, the question typically is whether the treatment is efficacious under ideal, rather than real-world, settings. The results of such studies, therefore, are not necessarily generalizable to all patients or situations. CER is intended to complement this approach by helping patients and clinicians make decisions about which treatment is the best choice in given situations. CER also is called patient-centered health research or patient-centered outcomes research to illustrate its focus on patient needs.[56]

NIH has a long history of supporting landmark CER studies that challenge existing standards of clinical practice. NIH was awarded $400 million from the American Recovery and Reinvestment Act of 2009 (ARRA) for CER. A CER Coordinating Committee has been initiated to ensure optimal use of the recovery funds, make funding recommendations to the NIH Director, and develop a long-term CER research plan.

NIH investments are generating CER findings of public health significance, high relevance to clinical medicine, and scientific excellence. For example, the Spine Patient Outcomes Research Trial (SPORT) has helped answer questions

about how best to treat various types of chronic low-back pain. Before SPORT, patients and physicians lacked data that compared treatment outcomes that could be used to guide people who were conflicted about whether to undergo surgery; some were not sure surgery was worth the risk, and others feared that delaying surgery might cause even more damage. SPORT has demonstrated that, indeed, surgery is superior to nonoperative treatments for the most common causes of chronic, severe low back pain: intervertebral disk herniation and lumbar spinal stenosis with or without degenerative spondylolisthesis (the slipping of vertebrae). In addition, the study revealed that people who have one of these conditions are not subjecting themselves to further harm if they adopt a wait-and-see approach before committing to surgery.

The Spine Patient Outcomes Research Trial (SPORT) has helped answer questions about how best to treat various types of chronic low-back pain. This is an example of NIH's commitment to comparative effectiveness research.

CER studies are ideal for providing physicians with evidence-based guidance to help them identify the safest and most effective therapies for their patients. For example, the NIH-supported Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial simultaneously compared two cardiovascular treatment approaches and two diabetes control strategies to improve survival and to lower the risk of heart attacks and strokes. The study, published in 2009, demonstrated that neither early revascularization nor insulin sensitization was superior to the tested alternatives in terms of cardiovascular disease (CVD) event rates. However, among patients for whom bypass surgery was deemed to be the appropriate revascularization procedure, prompt revascularization reduced the rate of major, nonfatal CVD events such as heart attack and stroke.

Changing Clinical Practice

It is not enough merely to have the infrastructure needed to address the ambitious goal of implementing science-based interventions and practices in community settings. Strategies to encourage adoption of proven approaches and treatments also are needed, as well as ways to tailor such approaches to specific populations or even to individuals. For example, NIH has made significant advances in elucidating the scientific bases for the effects of several treatment approaches based on complementary and alternative medicine (CAM). However, results of a national survey designed to gauge the potential for CAM research to influence clinical practice revealed a need for more effective dissemination of research findings. Acupuncturists, naturopaths, internists, and rheumatologists were asked about their awareness of two major NIH-sponsored studies of acupuncture or glucosamine/chondroitin for treating osteoarthritis of the knee. According to the survey results published in 2009, more than half (59 percent) of the 1,561 respondents were aware of at least 1 of the 2 clinical trials, but only 23 percent were aware of both. Although CAM research has the potential to make a difference in both conventional and alternative medicine clinical practice, the survey points to the need to train all clinicians in interpretation and use of evidence from research studies and to improve the dissemination of research results.

NIH has made significant advances in elucidating the scientific bases for the effects of several treatment approaches based on complementary and alternative medicine.

In addition, NIH supports 13 Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging to improve the health, quality of life, and productivity of middle-aged and older people. The centers work to facilitate translation of basic behavioral and social science to practical outcomes by developing new technologies and by stimulating new use-inspired research (that is, research focused on meeting a societal need, usually for a device to improve quality of life for certain populations). Roybal investigators have made several key discoveries. One center, for example, has developed tools and technologies for identifying older adults at risk for automobile crash involvement and is working with industry partners to develop and disseminate products based on these tools. Another center has developed an electronic in-home assessment tool to facilitate early detection of changes in health or memory. Companies have used this model to develop related products, and the model has spurred several new NIH-funded research projects, including the development of a new medication tracker for older adults.

The Pharmacogenetics Research Network (PGRN) is ushering in the era of personalized medicine. The goal of pharmacogenetics research is to enable doctors to move beyond the current, one-size-fits-all approach to treatment and toward prescribing the drugs and dosages that will work best for each person. NIH established the PGRN to study how genes affect the way a person responds to medicines. The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), a component of the PGRN, sponsors data-sharing consortia. The International Tamoxifen Pharmacogenetics Consortium is gathering genetic and clinical data on the efficacy and toxicity of tamoxifen from patients around the world to test for specific associations between genetic variants and clinical effects. The International Severe Irinotecan Neutropenia Consortium is assembling a large data set to definitively answer questions relating to genetic effects on adverse outcomes of irinotecan anticancer therapy and to provide tools for evaluating toxicity risk.

Disseminating Research Findings

NIH produces the PubMed/MEDLINE database, the world's most heavily used source of information about research findings published in journal articles. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.) NIH also is taking the lead in special efforts to inform the public and health care practitioners about research results that have the potential to improve health (also see the section on *Health Communication and Information Campaigns and Clearinghouses* in Chapter 3). The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational materials on diabetes and kidney disease, respectively. For example, the NDEP disseminates the results of the DPP by encouraging people to take small steps to prevent type 2 diabetes. The NDEP also promotes the importance of comprehensive diabetes control in an educational campaign, "Control Your Diabetes. For Life." The NKDEP encourages African American families to discuss kidney disease at family reunions, and also provides tools and resources for health care providers to coordinate care and improve patient outcomes for kidney disease. Both programs tailor materials for minority groups that are disproportionately burdened by kidney disease, type 2 diabetes, and obesity.

In keeping with the NIH Public Access Policy (also see the sections on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3), scientists are required to submit final, peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central. This practice ensures that the public has access to the published results of NIH-funded research to help advance science and improve human health.

Located in the NIH Office of the Director, the Office of Medical Applications of Research (OMAR) works closely with ICs to assess, translate, and disseminate the results of biomedical research that can be used in the delivery of health services. OMAR coordinates periodic consensus conferences with the goal of reviewing areas of NIH-supported research where there may be a gap between research accomplishments and clinical care. To date, NIH has conducted more than 120 consensus development conferences and 30 state-of-the-science conferences. Consensus and state-of-the-science statements are disseminated widely after the conference either to modify clinical practice when evidence strongly supports the use (or avoidance) of a particular intervention or to direct future research when important gaps in knowledge have been identified. The consensus statements that result from these conferences are shared widely with health care providers, policymakers, patients, and the media. In 2008, consensus statements were issued on hydroxyurea treatment for sickle cell disease and on the management of hepatitis B. In 2009, state-of-the-science statements were released on the use of family histories in the primary care setting and on the diagnosis and management of ductal carcinoma in situ.

In its quest to help clinicians and patients make appropriate decisions about health care, NIH periodically convenes expert panels that review the cumulative research and publish evidence-based clinical practice guidelines that describe a range of generally accepted approaches for the diagnosis, management, or prevention of specific diseases or conditions. In addition, NIH clinical guidelines provide recommendations that patients and their doctors can use to develop individual treatment plans tailored to the specific needs and circumstances of the patient. In 2009, two new guidelines for the prevention and treatment of HIV-associated co-infections were issued: *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents* and *Guidelines for the Prevention and Treatment of Opportunistic*

Infections Among HIV-Exposed and HIV-Infected Children. The Pediatric Cardiovascular Risk Reduction Initiative guideline is slated for release in mid 2010.

In its quest to help clinicians and patients make appropriate decisions about health care, NIH periodically convenes expert panels that review the cumulative research and publish evidence-based clinical practice guidelines. The Pediatric Cardiovascular Risk Reduction Initiative guideline is slated for release in mid-2010.

Bolstering the Research Continuum

NIH is committed to restructuring the clinical research enterprise, a key objective of the NIH Roadmap for Medical Research, which comprises a series of initiatives funded by the NIH Common Fund. These high-impact initiatives are designed to pursue major opportunities and gaps in biomedical research that no single NIH institute could tackle alone, but which the agency as a whole can address to make the biggest impact possible on the progress of medical research. To accelerate and strengthen the clinical research process, a set of NIH Roadmap initiatives will work toward improving the clinical research enterprise by adopting a systematic infrastructure that will better serve the evolving field.

Building Capacity for Clinical and Translational Research

Drawing on the momentum of the NIH Roadmap and extensive community input, the Clinical and Translational Science Award (CTSA) program is creating academic homes for the discipline of clinical and translational science at institutions across the country. As of fall 2009, this network of research institutions consists of 46 awardees in 26 states. The consortium will eventually link about 60 institutions around the Nation. The program encourages the development of novel methods and approaches to clinical and translational research, enhances informatics and technology resources, and improves training and mentoring to ensure that new investigators can navigate an increasingly complex research system. CTSAs are enabling researchers to work in unprecedented ways to advance medical research across many disease areas and conditions, including cancer, neurological diseases, cardiovascular disease, diabetes, and obesity.

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A key ingredient in research success is the translation of laboratory bench insights to the patient bedside and back again, to inspire new laboratory investigations that ultimately improve patient care and public health. In this vein, the Centers of Research Translation (CORT) program was launched to unite basic and clinical research. Each CORT encompasses at least three projects, including one clinical and one basic research study. The three most recently funded CORTs are the Center for Genetic Dissection of SLE (lupus), the Center for New Approaches to Assess and Forestall Osteoarthritis in Injured Joints, and the Center for Psoriasis Research Translation.

Researchers are increasingly conducting studies in community clinics, doctors' offices, and other health care facilities as innovative means of building capacity across the Nation and ensuring that diverse populations are involved in research. For example, NIH fosters scientifically rigorous research in oral health care in three dental practice-based research networks (PBRNs) to address the longstanding lack of high-quality research data to guide everyday treatment decisions in the dentist's office. The PBRNs have developed multiple methods of delivering research training to practicing clinicians, including training in research methods, protection of human participants, good clinical practice, research protocol development, and interpretation of research results. Descriptions of the training programs have been reported in national journals, and a collaboratively written chapter recently was accepted for publication in a textbook on PBRNs. Over the course of the grant period, the networks will each complete approximately 15 to 20 short studies, several of which have already been reported in the scientific literature.

Developing the Research Teams of the Future

Through its career development initiatives, NIH is preparing to meet the need for a multidisciplinary, well-trained cadre of researchers at every point in the research continuum. (Also see the section on *Research Training and Career Development* in Chapter 3.) For example, a key component of the CTSA program is the creation of graduate degree-granting and postgraduate programs in clinical and translational science, which will provide an enriched environment for educating and retaining the next generation of clinical and translational researchers.

In addition, NIH develops, administers, and evaluates clinical research training initiatives that contribute to the professional growth of the clinical and translational research community, including medical and dental students, physicians in residency and in fellowship programs, established investigators, allied health professionals, and community partners. A clinical research curriculum is offered at NIH and other domestic and international locations. Extramural researchers have a new opportunity to access rich training experiences via a "Clinical Research Management Sabbatical," designed to help them develop leadership skills for conducting clinical research. Partnerships between NIH and extramural collaborators and industry have contributed to the menu of educational offerings. For example, via videoconferencing, Duke University School of Medicine offers NIH physicians and dentists an opportunity to receive a master's degree of health sciences in clinical research. The intramural Clinical Research Training Program, a partnership supported by NIH and a grant to the Foundation for the NIH from Pfizer, Inc., trains 30 advanced medical and dental students annually in clinical or translational research.

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The Research Centers in Minority Institutions (RCMI) program develops and enhances the research infrastructure of minority institutions by expanding human and physical resources for conducting basic, clinical, and translational research. The program, which began in 1985 in response to congressional report language (see the description of the RCMI program in the notable examples that follow under the theme "Bolstering the Research Continuum"), provides grants to institutions that award doctoral degrees in the health professions or health-related sciences and have enrollments that are predominantly students from minority communities underrepresented in the biomedical sciences. The RCMI Translational Research Network (RTRN) is a national consortium of clinical and translational researchers in the RCMI Centers, working in collaboration with investigators from other academic health centers, community health providers, and the public to focus their collective efforts on addressing health disparities. RTRN researchers focus on diseases that disproportionately affect minority and other medically underserved populations. The multisite collaborative research supported by RTRN infrastructure, training, and resources is ensuring that discoveries generated in the laboratory are being translated into clinical studies. (Also see the section on *Minority Health and Health Disparities* in Chapter 2.)

The RCMI Clinical Research Education and Career Development (CRECD) Awards provide didactic training and mentored clinical research experiences to develop independent researchers who can lead clinical research studies, especially those addressing health disparities. RCMI CRECD awards help develop and implement degree programs in minority institutions that train doctoral and postdoctoral candidates in clinical research.

Improving Research Efficiency

Maximizing human subject protection, while facilitating translational and applied clinical research, has become a critical challenge in the 21st century. To increase the efficiency and effectiveness of the clinical research enterprise, NIH is examining barriers to clinical research and striving to harmonize regulations and policies that pertain to its conduct and oversight.

The NIH Clinical Research Policy Analysis and Coordination (CRpac) program is a focal point for streamlining and optimizing policies and requirements concerning the conduct and oversight of clinical research.

The NIH Clinical Research Policy Analysis and Coordination (CRpac) program is a focal point for streamlining and optimizing policies and requirements concerning the conduct and oversight of clinical research. As the lead Federal agency supporting clinical research, it is incumbent upon NIH to promote the efficiency and effectiveness of the clinical research enterprise by facilitating compliance and oversight. The CRpac program works on an array of issues and activities usually in close collaboration with other Federal agencies and offices that have responsibilities concerning the oversight of clinical research. NIH also is partnering with several other Federal agencies to ensure that a standard reporting format is available for investigators to report adverse events associated with their clinical research. The development of the Basal Adverse Event Report (BAER) will allow investigators to satisfy the different safety reporting requirements for all Federal agencies. NIH also has specific initiatives to restructure the clinical trials enterprise in the area of oncology. For example, the Standard Terms of Agreement for Research Trials are designed to help cut the time spent on contract negotiations between pharmaceutical/biotechnology companies and academic medical centers. In addition, the Clinical Trials Reporting Program is establishing a comprehensive database containing regularly updated information on all NCI-funded interventional clinical trials. Grantees are requested to enter specific information about each clinical trial into the database. This information will be used to coordinate research efforts to optimize the Nation's investment in cancer research.

Conclusion

The results of NIH's commitment to clinical and translational science are apparent in the following highlights describing some of the important accomplishments and ongoing initiatives in these rapidly developing areas of research.

Notable Examples of NIH Activity

Key
E = Supported through **E**xtramural research I = Supported through **I**ntramural research O = **O**ther (e.g., policy, planning, or communication) COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct IC acronyms in **bold** face indicate lead IC(s).

Preclinical Research: Translating Basic Science Discoveries to Human Studies

New Therapeutic Strategy for Retinitis Pigmentosa: Retinitis pigmentosa (RP) is a set of genetic diseases that cause the death of rod photoreceptors, the light-sensitive cells in the peripheral retina that help us see in dark and dimly lit environments. Unfortunately, the death of rod cells causes the death and degeneration of healthy cone cells. Cone photoreceptors provide sharp visual acuity, allowing us to read, recognize faces, drive a car, or perform other daily tasks that require hand-eye coordination. If cone cells could be preserved, patients with RP could avoid severe impairment. Mounting evidence suggests that cone cells die due to oxidative damage because the blood vessels in the retina cannot regulate blood flow to reflect decreased oxygen demand after rod cell death. NIH-supported investigators recently began efforts to bolster innate production of antioxidants by overexpressing genes that defend against oxidative assault. In a novel set of experiments, investigators developed a mouse strain with RP that also overexpressed various genes involved

in the antioxidant defense system. Overexpression of superoxide dismutase 2 (SOD2) and catalase, two powerful antioxidant enzymes, preserved cone cells. These findings support the concept of a gene-based treatment strategy to strengthen the body's antioxidant defense system in patients with RP.

→ Usui S, et al. *Mol Ther* 2009;17(5):778-86. PMID: 19293779.
→ For more information, see http://www.nature.com/mt/journal/v17/n5/abs/mt200947a.html
→ (E) (**NEI**)

Translational Research on Alzheimer's Disease (AD): To move basic research on AD and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. A number of agents are undergoing testing, including antihypertensives, anti-inflammatory drugs, and novel small molecules. In addition, in recent years, NIH-supported basic research has contributed to industry development of new Alzheimer's disease drugs. This program is a cornerstone of the NIH GPRA goal to "by 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-048.html
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIA**) (GPRA)

Lupus: There have been significant advances in identifying disease risk genes for systemic lupus erythematosus (lupus) in recent years. Genome-wide association, linkage analysis, and direct sequencing have revealed genetic variations in lupus patients for molecules involved in immune mechanisms and regulation, inflammation, and vascular cell activities. The disease affects women disproportionately, with female lupus patients outnumbering males nine to one. African American women are three times as likely to get lupus as Caucasian women, and it also is common more in Hispanic, Asian, and American Indian women. These results are being replicated in distinct racial and ethnic populations. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects. Another critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by government agencies, private foundations, and industry. The numerous genes uncovered in these studies reflect the complex expression of lupus, which varies from patient to patient. For example, a variant in an immune regulatory gene specifically is associated with severe forms of lupus that include kidney disease, but not skin manifestations. Methods to analyze patients' blood samples are being developed to group disease-specific variations in gene expression according to pathogenic mechanisms. This system may be used to predict flares of lupus activity in the future and guide individualized treatment. Lupus risk genes also have been discovered on the X chromosome and reproduced in animal models of the disease. These important findings shed light on the female predominance of lupus.

→ Edberg JC, et al. *Hum Mol Genet* 2008 Apr 15;17(8):1147-55. PMID: 18182444.
Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), et al. *Nat Genet* 2008;40(2):204-10. PMID: 18204446.
Taylor KE, et al. *PLoS Genet* 2008;4(5):e1000084. PMID: 18516230. PMCID: PMC2377340.
Chaussabel D, et al. *Immunity* 2008;29(1):150-64. PMID: 18631455. PMCID: PMC2727981.
Smith-Bouvier DL, et al. *J Exp Med* 2008;205(5):1099-108. PMID: 18443225. PMCID: PMC2373842.
Scofield RH, et al. *Arthritis Rheum* 2008;58(8):2511-7. PMID: 18668569.
Jacob CO, et al. *Proc Natl Acad Sci U S A* 2009;106(15):6256-61. PMID: 19329491. PMCID: PMC2669395.

→ This example also appears in Chapter 2: *Autoimmune Diseases*, Chapter 2: *Minority Health and Health Disparities*, Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*
→ (E/I) (**NIAMS**, NCI, NCRR, NHLBI, NIAID, NIDCR, NINDS)

Addressing the Heterogeneity of Autism Spectrum Disorders: NIH released a series of Funding Opportunity Announcements (FOAs), supported by funds from the American Recovery and Reinvestment Act of 2009, soliciting applications for 2-year research projects to address the heterogeneity of Autism Spectrum Disorders (ASD). This initiative represents the largest NIH funding opportunity for research on ASD to date and will jump-start many of the short-term objectives set forth in the Interagency Autism Coordinating Committee's Strategic Plan for Autism Spectrum Disorder Research. The FOAs target research in areas such as measurement development, biomarkers, immune and central nervous systems interactions, genetics, environmental risk factors, model development, treatment and intervention, and services research.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-170.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-171.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-172.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-173.html
→ For more information, see http://www.nimh.nih.gov/science-news/2009/rising-to-the-challenge-nih-will-use-60-million-in-recovery-act-funds-to-support-strategic-autism-research.shtml
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIMH**, NICHD, NIDCD, NIEHS, NINDS) (ARRA)

Pediatric Rheumatic Diseases: A rare, genetically inherited, inflammatory condition recently was discovered by researchers from NIH and other institutions. DIRA ("deficiency of the interleukin-1 receptor antagonist") patients often are misdiagnosed and do not receive appropriate treatment because their disease is characterized by symptoms seen in many illnesses: recurring episodes of systemic inflammation in multiple tissues, such as skin, bones, and joints. Inflammation is crucial in fighting infections, but uncontrolled, chronic inflammation can cause organ and tissue damage. It was found that DIRA symptoms are caused by a defective gene for a protein (IL-1Ra) that normally inhibits molecular signals for inflammation. Understanding DIRA symptoms and pathogenesis can guide better treatment for the disease, and may help clarify the IL-1Ra gene's role in promoting inflammation in more common diseases. On another front, children with lupus have a significantly increased risk for cardiovascular complications related to premature atherosclerosis, which is a potential source of long-term morbidity and mortality. Statins are drugs that lower cholesterol in blood and decrease the risk for atherosclerosis and cardiovascular disease. Statins also have intrinsic anti-inflammatory properties. The Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial has been testing whether statins can delay the progression of arterial thickening from atherosclerosis in children diagnosed with lupus. Another prospective study of adult and pediatric lupus patients confirmed previous observations, that children have more active disease than adults at the time of diagnosis. Over time, pediatric lupus patients also have more aggressive and severe disease than adult lupus patients.

→ Aksentijevich I, et al. *N Engl J Med* 2009;360(23):2426-37. PMID: 19494218. PMCID: PMC2876877. Brunner HI, et al. *Arthritis Rheum* 2008;58(2):556-62. PMID: 18240232.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2009/06_03.asp
→ This example also appears in Chapter 2: *Autoimmune Diseases*
→ (E/I) (**NIAMS**)

New Indications for Established Agents to Treat Chronic Disease: When identifying interventions to treat an illness or chronic condition, testing drugs that already have been developed for other conditions sometimes can be faster and more cost-effective than designing entirely new agents because drug safety profiles already have been established, and contraindications already are known. NIH intramural investigators currently are exploring the use of several established agents in the treatment of chronic disease. For example, a growing body of animal research suggests that the compound fenoterol, widely used for treatment of pulmonary disease, may be effective in the treatment of congestive heart failure. Experimental results with fenoterol are sufficiently encouraging to recommend advancing translational efforts and planning clinical trials. Other studies in animal models have shown that the drug erythropoietin, used to treat certain types of anemia, has a protective effect on the heart if administered shortly after a heart attack. Based on the results of these studies, researchers have initiated a study to assess the effects of erythropoietin (EPO) on the heart after a heart attack. Researchers also have reported preclinical data that suggest a therapeutic benefit of the diabetes drug exendin-4 in the treatment of stroke and Parkinson's disease.

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (I) (**NIA**)

NIH Countermeasures Against Chemical Threats (CounterACT) Research Program: The CounterACT Research Network, as reflected in an NIH GPRA goal, develops medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The Network, which has collaborated with the U.S. Department of Defense (DOD) from its inception in 2006, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. One promising countermeasure, midazolam, which DOD researchers identified as a potential countermeasure against chemical agent-induced seizures, has entered clinical trials through the NIH Neurological Emergency Clinical Trials Network, and NIH is collaborating with DOD to complete animal studies necessary for its FDA approval as a nerve agent treatment. The New Drug Application is expected early FY 2010, with approval anticipated by the end of the year. The Network also has developed six other lead compounds as therapeutics for cyanide, nerve agent, chlorine, and sulfur mustard, and has participated in pre-Investigational New Drug application meetings with FDA related to these efforts. One of the diagnostic devices developed by the program is being used in an NIH clinical trial. Three chemical agent therapeutics developed by the program also show promise as therapies for radiation exposures, and the program is collaborating with the NIH Medical Countermeasures Against Radiological and Nuclear Threats program.

→ For more information, see http://www.ninds.nih.gov/research/counterterrorism/counterACT_home.htm
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00809146
→ For more information, see http://nett.umich.edu/nett/welcome
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NINDS**, NEI, NIAID, NIAMS, NICHD, NIEHS, NIGMS) (GPRA)

Peripheral Neuropathies: NIH funds studies focused on understanding the genetic basis and molecular and cellular mechanisms of many peripheral neuropathies, including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, inherited neuropathies such as Charcot-Marie-Tooth, inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy, and rare forms of peripheral neuropathy. Other notable projects include a natural history study of diabetic neuropathy, projects to improve the efficiency and effectiveness of diagnosis for various peripheral neuropathies, and a Phase III clinical trial to treat Familial Amyloidotic Polyneuropathy. In August 2008, a pair of program announcements was released to promote translational research in neuromuscular disease. Diseases included in these program announcements are those that affect the motor unit—the motoneuron, its process (axon), and the skeletal

muscle fiber that is innervated by the neuron—such as peripheral neuropathy, amyotrophic lateral sclerosis, and muscular dystrophy. This unique structure-function framework provides a coordinated approach for therapeutic development in a subset of neurological diseases that share many common features, including the peripheral neuropathies.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NINDS**, NIDDK)

Programs to Accelerate Medication Development for Alcoholism Treatment: Alcohol dependence is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ among individuals. Therefore, a diverse repertoire of medications is needed to provide effective therapy to a broad spectrum of alcohol-dependent individuals. Although promising compounds have been identified, developing medications is a long and costly process with a low probability of success for any single agent. NIH has initiated collaborations with the pharmaceutical industry to ensure its interest in taking promising compounds through the final phase of clinical trials and subsequent FDA consideration. As part of this approach, two new programs have been initiated:

- Laboratories have been established to screen promising compounds with animal models, enabling faster determination of those that merit advancement to large, multisite studies. Animal studies already have produced several targets for human studies that now are underway. The animal models are being validated using medications that have been tested clinically.
- A network of sites is being developed to conduct early Phase II proof-of-concept human trials. NIH will encourage the pharmaceutical industry to screen proprietary compounds in the preclinical models and, when results are positive, test them in the early Phase II human trials network. Currently quetiapine and levetiracetam are being evaluated in this network.
- Pharmacogenetic studies are ongoing to determine genetic variants that predict success for various medications.

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E/I) (**NIAAA**) (GPRA)

Translational Research with Gene Transfer for X-Linked Juvenile Retinoschisis (XLRS), a Congenital Eye Disease of Boys: XLRS is a rare but severe developmental abnormality of the retina found in children that causes impaired visual acuity and retinal detachment. Clinical examination shows small cysts within the macula, the center of the retina, and a splitting (or schisis) of the layers of the peripheral retina. XLRS is caused by a mutation in a single gene, retinoschisin, which is thought to play a structural role in the retina. NIH intramural investigators are developing gene transfer therapy to ameliorate and possibly cure XLRS. In other gene transfer clinical trials for Leber congenital amaurosis, a single subretinal injection of the gene-carrying vector reached about 25 percent of the retina. However, subretinal injection is unsuitable for XLRS as the retina is too fragile and the entire retina needs treatment to prevent further schisis. To this end, NIH intramural investigators injected a vector containing copies of the retinoschisin gene into the vitreous, the clear, jelly-like fluid inside the eye, using a mouse model of XLRS. This allowed retinoschisin to penetrate the entire retina in amounts similar to healthy retinas. Treated mice demonstrated a decrease in schisis and showed improved retinal activity 11-15 weeks after treatment. This study offers evidence that injection into the vitreous is a viable method to deliver gene therapy to the neural retina.

→ Park TK, et al. *Gene Ther* 2009;16:916-26. PMID: 19458650. PMCID: PMC2774250.
→ For more information, see http://www.nature.com/gt/journal/v16/n7/full/gt200961a.html
→ (I) (**NEI**, NIDCD)

The NIH Rapid Access to Intervention Development (RAID) Program: The NIH-RAID program makes available, on a competitive basis and at no cost to investigators, certain critical resources needed to develop new therapeutic agents, including not only laboratory services but also expertise in the regulatory process. The program directly addresses roadblocks to moving research findings from bench to bedside. Among the projects approved are potential therapies for hepatic fibrosis, sickle cell anemia, drug abuse, and Crohn's disease. The NIH-RAID program is part of the NIH Roadmap for Medical Research.

→ For more information, see http://nihroadmap.nih.gov/raid/index.aspx
→ (E) (**NINDS**, Common Fund - all ICs participate)

Translational Research for Neurological Disorders: The Anticonvulsant Screening Program has catalyzed the development of six epilepsy drugs now on the market; the Neural Prosthesis Program has pioneered devices to restore lost nervous system functions; the Intramural Program has developed the first enzyme therapy for inherited disorders; and investigator-initiated research programs have led to development of FDA-approved drugs by industry. In 2003, NIH launched a program designed to expedite preclinical therapy development across all neurological disorders. The Cooperative Program in Translational Research supports academic and small business investigator-initiated projects in single laboratories or consortia, using milestone-driven funding and peer review tailored to the requirements of therapy development. Projects are developing drug, stem cell, or gene therapies for amyotrophic lateral sclerosis (ALS), Batten disease, epilepsy, Huntington's disease, muscular dystrophies, Parkinson's disease, tuberous sclerosis, and stroke, among other disorders. NIH also has developed several focused translational research initiatives over the last decade. The Spinal Muscular Atrophy (SMA) Project, for example, is an innovative pilot program to develop a treatment for SMA using a "virtual pharma" strategy that engages resources to carry out a drug development plan via contracts and collaboration. The project has two patents on compounds that show promise and is evaluating the safety of the most promising drug candidates, with the goal to begin human clinical trials as soon as possible. Translational research is a "signature project" for NINDS investment of American Recovery and Reinvestment Act funds.

→ For more information, see http://www.ninds.nih.gov/funding/research/translational/index.htm.
→ For more information, see http://www.ninds.nih.gov/research/asp/index.htm
→ For more information, see http://www.ninds.nih.gov/research/translational/index.htm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E) (**NINDS**) (ARRA)

Confronting the Challenge of Antimicrobial Resistance: Antimicrobial resistance has become a major public health threat that is severely jeopardizing the utility of many "first-line" antimicrobial agents. The development of resistance can be caused by many factors, including the inappropriate use of antibiotics. NIH supports a robust basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes. NIH also is pursuing translational and clinical research in this area, including clinical studies to test interventions for community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection and to evaluate the efficacy of off-patent antimicrobial agents. NIH laboratories are at the forefront of understanding the fundamental causes of resistance—from studies of the disease-causing organisms and the progression of disease to research on the advantages and shortcomings of current antibiotics. Specific research foci of NIH researchers and NIH-supported grantees include MRSA and vancomycin-resistant *Staphylococcus aureus* (VRSA) (commonly acquired in community settings), and drug-resistant malaria and tuberculosis. NIH supports genomic sequencing through its Microbial Sequencing Centers; researchers at these centers have sequenced the genomes of numerous disease-causing bacteria, viruses, parasites, and fungi, which may help identify mechanisms of resistance and when and where resistance emerges.

→ For more information, see http://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Genomics*
→ (E/I) (**NIAID**) (GPRA)

Development and Testing of Malaria Vaccines and Therapeutics: NIH supports recent calls to work toward the goal of malaria eradication. Means toward this end include stopping the spread of the malaria parasite, reducing the burden of disease region by region, and eliminating the parasite from malaria-endemic countries and then from every country throughout the world. In FY 2008, NIH assessed its malaria research portfolio and identified opportunities for the next phase of malaria research. This led to the publication of the Strategic Plan for Malaria Research and the related NIAID Research Agenda for Malaria. NIH recently launched a new initiative, the International Centers of Excellence in Malaria Research, to support a novel, global, multidisciplinary approach to understanding malaria in the evolving context of control, elimination, and eradication. NIH researchers recently began clinical investigations to assess malaria biology and pathogenesis with collaborators in Mali and Cambodia, activities that resulted in the completion (or expansion) of research facilities and hospitals to support new malaria research programs. Examples of NIH-supported advances in malaria research include:

- Successfully decoding the genome of the parasite that causes relapsing malaria and determining that the anti-malarial drug, chloroquine, may once again be used to prevent malaria in African children.
- Investigating novel vaccine strategies, such as those that block transmission of the malaria parasite to the mosquito vector, and exploring the molecular biology of the parasite and its interaction with humans.

Ten vaccine candidates currently are in preclinical development and five are in clinical trials.

→ For more information, see http://www3.niaid.nih.gov/topics/Malaria/
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E/I) (**NIAID**)

Medical Countermeasures Against Nuclear and Radiological Threats: NIH continues to lead the HHS effort to sponsor and coordinate research to develop medical countermeasures to mitigate and/or treat radiation-induced damage. Many candidate medical countermeasures are in the early stages of discovery; however, substantial effort focuses on later development as lead compounds are identified. Animal model testing is underway for 59 medical countermeasures for hematopoietic (HE) acute radiation syndrome (ARS), 18 for gastrointestinal (GI) ARS, 13 for radiation-induced lung pneumonitis and/or fibrosis, 13 for kidney injury, 7 for brain injury, and 17 for skin, including combined injuries (radiation plus burns or wounds). Three orally bioavailable forms of diethylenetriaminepentaacetic acid (DTPA), which may be used to treat victims with internal radionuclide contamination from fallout or "dirty bombs," are in development. Research into 6 lead, orally bioavailable compounds with enhanced properties for removing radioactive isotopes from the body also is ongoing. Interactions with 87 biotechnology companies through an advanced development contract have led to the identification and initial animal efficacy confirmation for 7 HE-ARS candidate medical countermeasures and 2 GI-ARS candidate medical countermeasures. Other areas of research include characterization of genomic, proteomic, metabolomic and cytogenetic markers of radiation injury, and development of biodosimetry devices to provide accurate and timely radiation exposure information to assist in medical triage and treatment strategies.

→ For more information, see http://www3.niaid.nih.gov/topics/radnuc/
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIAID**) (ARRA)

Rapid Research Response to Emerging Disease Threats: The sudden and unpredictable emergence of infectious diseases requires advance preparation to safeguard public health. Because the groundwork of basic research can be crucial when new health threats arise, NIH conducts and supports research to increase basic knowledge of infectious diseases, and advance development of effective diagnostics, therapeutics, and vaccines. In the case of severe acute respiratory syndrome (SARS), for instance, NIH's broad portfolio of basic research grants on coronaviruses was critical to understanding the new pathogen. NIH has developed new funding initiatives for accelerated, targeted research to encourage collaborative and product development-oriented projects. NIH also provides needed infrastructure and resources to support the research community in the event of a public health emergency. For example, the national network of Vaccine and Treatment Evaluation Units provides a ready means to conduct clinical trials to evaluate vaccines and treatments for outbreaks such as the novel 2009 H1N1 influenza. In 2009, NIH awarded new funding for 1 and renewed funding for 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs). The RCEs are a critical component of the U.S. research infrastructure for infectious diseases, and are designed to respond flexibly to changing scientific needs and priorities. RCE researchers are developing new or improved ways to treat, diagnose, or prevent illnesses, including anthrax, West Nile fever, plague, and dengue fever. The RCEs are prepared to provide scientific expertise to first responders in an infectious disease-related emergency, whether such an emergency arises naturally or through an act of bioterrorism.

→ For more information, see http://www3.niaid.nih.gov/LabsAndResources/resources/rce/default.htm
→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/RCEs_ARRA.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E/I) (**NIAID**) (ARRA)

Renewed Focus on Basic HIV Vaccine Discovery Research: In March 2008, NIH sponsored a Summit on HIV Vaccine Research and Development. Participants reached consensus that NIH should increase its emphasis on basic vaccine discovery research. Toward this end, the Highly Innovative Tactics to Interrupt Transmission of HIV program was established to stimulate research on novel, unconventional, "outside the box," high-risk, high-potential, and high-impact approaches that might provide long-term protection from HIV acquisition. The Basic HIV Discovery Research initiative also was initiated to support generation of knowledge that will inform new conceptual approaches to HIV vaccine design. NIH also funds new research through the B Cell Immunology for Protective HIV-1 Vaccine program to foster fundamental research on B cell immunology to derive new understanding and approaches for development of HIV vaccines. NIH continues to conduct clinical research as appropriate and seeks to answer basic research questions through clinical trials. NIH recently launched an exploratory clinical trial through the HIV Vaccine Trials Network to examine whether a two-part vaccine regimen can decrease viral load in vaccinated male study participants who later become infected with HIV. It is hoped that this study will answer important scientific questions that could lead to the discovery and development of new and improved HIV vaccine candidates.

→ For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/research/
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-024.html
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIAID**) (GPRA)

Tackling Neglected Tropical Diseases: Neglected tropical diseases (NTDs) such as lymphatic filariasis, schistosomiasis, leishmaniasis, and dengue take a tremendous toll on global health. The World Health Organization estimates that more than 1 billion people—approximately one-sixth of the world's population—suffer from at least 1 NTD. NIH scientists and NIH-supported researchers in countries where NTDs are widespread are developing vaccines and treatments for diseases such as leishmaniasis and identifying new drugs for sleeping sickness and Chagas' disease. NIH-supported researchers also have made a significant leap forward in the battle against schistosomiasis by identifying potential new therapies through the use of genomics and medicinal chemistry. The Vector Biology Research Program supports research

on several vectors that transmit agents of NTDs. Through this program, a project in French Polynesia aims to reduce populations of *Aedes polynesiensis*, a mosquito species responsible for spreading filariasis. Other investigators studying the mosquito immune response against filarial worms hope to identify targets for blocking development of the worm inside the mosquito. NIH scientists studying the salivary proteome of NTD vectors are identifying novel biologically active compounds and vaccine targets. In FY 2009, NIH-supported researchers reported the first complete genome sequences for two parasite species that cause schistosomiasis. Finally, a public-private partnerships for product development program is designed to accelerate research and development of new diagnostic, preventive, therapeutic, and control strategies for infectious diseases of global importance for which commercial markets currently provide insufficient incentive for corporate investment.

→ For more information, see http://www3.niaid.nih.gov/topics/tropicalDiseases/default.htm
→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/schisto_genomes.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E/I) (**NIAID**)

Three-Pronged Approach to Fighting HIV: The unique and formidable challenge of combating HIV is spurring leaders in medicine and public health to consider a bold new approach to fighting it. NIH and other organizations are exploring a three-pronged approach to fight the HIV/AIDS pandemic. The first prong is pre-exposure prophylaxis (PrEP), which uses antiretroviral therapies to prevent HIV infection among people who are not infected with HIV but who are at high risk of becoming infected. NIH currently is testing this approach in clinical trials such as the iPREX study, which is examining whether the HIV treatment Truvada can prevent HIV infection among HIV-negative men who have sex with men. The second prong is a novel approach, based on mathematical modeling, which suggests that the implementation of a universal HIV testing program and the immediate initiation of antiretroviral therapy (ART) for those individuals who test positive could dramatically reduce the number of new HIV cases within the decade. NIH now is addressing a number of critical scientific issues to determine the feasibility of this approach. Finally, NIH is strongly encouraging research to cure HIV by eliminating HIV reservoirs, pockets of undetectable latent and persistent HIV, which exist even in people on ART who have an undetectable viral load. Stopping ART treatment results in a rebound of viral load to levels seen prior to treatment. NIH has launched a new initiative to identify these reservoirs and develop techniques to eradicate them.

→ Paltiel AD, et al. *Clin Infect Dis* 2009;48(6):806-15. PMID: 19193111.
Dieffenbach CW, Fauci AS. *JAMA* 2009;301(22):2380-2. PMID: 19509386.
→ For more information, see http://www.washingtonpost.com/wp-dyn/content/article/2009/04/15/AR2009041503040.html
→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/test_treat.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIAID**) (ARRA)

2009 H1N1—Responding to Pandemic Influenza: NIH is engaged fully in the government-wide effort to understand the 2009 H1N1 virus and rapidly develop countermeasures. Activities are being conducted in NIH-supported research networks such as the Centers of Excellence in Influenza Research and Surveillance (CEIRS) and Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs), as well as by industry partners and individual NIH grantees. NIH used its longstanding vaccine clinical trials infrastructure—notably, the network of Vaccine and Treatment Evaluation Units—to quickly evaluate pilot lots of vaccine candidates for safety and ability to induce protective immune responses, and to determine the appropriate dose and number of dosages. Because of increased resistance to existing antiviral therapeutics, NIH is working to develop the next generation of influenza therapeutics/antivirals. Three drugs now in clinical testing include a long-acting neuraminidase inhibitor, an inhibitor of the enzyme that replicates viral genes, and a drug that prevents the virus from entering human lung cells. NIH will evaluate how well these candidate antiviral drugs block the 2009 H1N1 strain and will screen other compounds for activity against the virus. NIH also is developing

diagnostic platforms that can rapidly identify a wide variety of pathogens in clinical samples, including specific subtypes of influenza. NIH is accelerating development of these platforms to provide improved diagnostics for 2009 H1N1 influenza. In addition, enrollment is complete for an NIH pandemic influenza H1N1 DNA vaccine Phase I clinical trial that has begun, and NIH scientists are conducting basic research to develop universal influenza vaccines that can protect against multiple influenza strains.

→ For more information, see http://www3.niaid.nih.gov/topics/Flu/understandingFlu/2009h1n1.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E/I) (**NIAID**)

Preclinical Disease Models Informatics: Preclinical research results derived from animal models are an essential element in the decisional process to determine whether a basic science discovery should be considered as a potential therapeutic approach worthy of future development. Scientists who work with animal models can look forward to a new online tool designed to increase research efficiency, improve collaboration, and ultimately help bridge the gap between basic science and human medicine. With funding from NIH, the Linking Animal Models to Human Disease Initiative (LAMHDI) will integrate data and information about animal models and make them available to health researchers. LAMHDI creators will develop a database and website designed to make it easier for the biomedical research community to locate, identify, apply, and build upon the most useful animal models for its research. The initiative grew out of the Animal Models: Informatics and Access meeting in August 2008. At this meeting, animal research and informatics experts explored ways to remove research barriers and to develop frameworks for effective computation on existing animal models data to facilitate medical progress. The $1.57 million NIH-funded project is supported by a contract to Turner Consulting Group, a strategy and information technology firm.

→ For more information, see http://www.ncrr.nih.gov/publications/comparative_medicine/animal_models_informatics_and_access.asp
→ (E) (**NCRR**)

Strategies to Manage and Prevent Food Allergies: Food allergy occurs in approximately 4.7 percent of children under 5 years of age and in 3.7 percent of children 5 to 17 years of age. Allergies to peanuts and tree nuts, the allergens most relevant to severe food allergy and anaphylaxis, occur in approximately 1 percent of children and adults. Severe whole-body allergic reactions, also known as anaphylaxis, are a frequent cause of emergency room visits, many of which are attributed to food allergy. Every year in the United States, it is estimated that there are approximately 15,000-30,000 episodes of food-induced anaphylaxis. NIH seeks to understand better both the immune system response to food allergies and how certain foods trigger an allergic reaction. Researchers in the United States and abroad are conducting clinical trials to improve management of allergy to cow's milk, egg, and peanut, and innovative clinical trials are assessing strategies to prevent development of peanut allergies. One important trial will determine whether early and regular consumption of a peanut snack by infants and very young children at risk of developing peanut allergy will promote tolerance and prevent the development of this allergy. In FY 2008, NIH sought to bring new investigators into the field through the Exploratory Investigations in Food Allergy initiative, which supports innovative pilot studies and developmental research on the mechanisms of food allergy. The program will be recompeted in FY 2010. During this period, NIH continued funding for the Consortium of Food Allergy Research, which supports basic, preclinical, and clinical research to assess the pathophysiology and natural history of food allergy-associated anaphylaxis and to develop interventions to prevent and treat food allergy.

→ For more information, see http://www3.niaid.nih.gov/topics/foodAllergy/default.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E/I) (**NIAID**)

Muscle Recovery After Exercise or Injury: NIH funds a robust research portfolio on a wide range of basic, translational, and clinical research projects in skeletal muscle biology and diseases. In the past 2 years, NIH-funded scientists have published several papers on compounds that improve muscle function and endurance in animals. They hope that this new knowledge can be applied to improve treatments for certain muscle disorders, frailty, obesity, and other conditions in which exercise is known to be helpful, but not always practical. For example, researchers have identified two drugs that, in mice, seem to confer many of the healthful benefits of long-term exercise by giving the animals more fat-burning muscle and better endurance. Their discovery built on earlier, more basic research, which identified a protein that regulates several fat-burning genes in muscle cells. Other researchers, exploring the role of a protein found in immature muscle cells, discovered that creatine supplements taken by athletes play an important role in muscle repair. Elsewhere, at the University of Iowa's Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center, scientists have identified a disrupted molecular pathway that leads to fatigue after even mild physical exertion in mice with muscular dystrophy. Their study demonstrated that a signaling pathway that regulates blood vessel constriction in skeletal muscle after mild exercise is defective in mouse models for Duchenne muscular dystrophy and other myopathies. This finding may lead to treatments for the post-activity exhaustion that strikes many people who have neuromuscular disorders.

→ Kobayashi YM, et al. *Nature* 2008;456(7221):511-5. PMID: 18953332. PMCID: PMC2588643.
Narkar VA, et al. *Cell* 2008;134(3):405-15. PMID: 18674809. PMCID: PMC2706130.
O'Connor RS, et al. *J Physiol* 2008;586(Pt 12):2841-53. PMID: 18420707. PMCID: PMC2517193.
→ For more information, see http://www.nih.gov/news/research_matters/august2008/08112008mouse.htm
→ For more information, see http://www.nih.gov/news/research_matters/november2008/11032008neuromuscular.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIAMS**, NCRR, NIA, NICHD, NINDS) (COE)

Toward Better Treatment for Muscular Dystrophy: NIH is pursuing multiple pathways to therapeutic development for the muscular dystrophies. NIH funded two new Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers in FY 2008: the Boston Biomedical Research Institute, which seeks to identify biomarkers that can be used in preclinical studies and clinical trials of potential facioscapulohumeral muscular dystrophy (FSHD) therapies, and a center at the University of North Carolina at Chapel Hill, which is developing and testing gene therapies for Duchenne muscular dystrophy (DMD) and other muscle disorders. Collectively, the Wellstone centers program is designed to accelerate the translation of fundamental scientific advances to the clinic (see Chapter 4) and to serve as a national resource for the muscular dystrophy community through core facilities and training programs. NIH funds multiple approaches to therapeutic development through projects outside of the Wellstone program, including a robust portfolio on translational research in muscular dystrophy. Research currently is solicited in this area through two Funding Opportunity Announcements (FOAs) released in 2008: Exploratory/Developmental Projects for Translational Research in Neuromuscular Disease (R21) and the Cooperative Program in Translational Research in Neuromuscular Disease (U01). Previous FOAs on Translational Research in Muscular Dystrophy resulted in a number of funded projects in this area, including projects to develop small molecule drugs and to develop effective gene therapy design and delivery approaches. Progress also is being made toward the GPRA goal to "advance two emerging strategies for treating muscular dystrophy to clinical trial readiness by 2013."

→ For more information, see http://www.wellstonemdcenters.nih.gov/
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-229.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-228.html
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E) (**NINDS**, NHLBI, NIAMS, NICHD) (COE, GPRA)

NIH Committee on the Science of Behavior Change (SOBC): A key national goal, at the scientific and policy level, is to eliminate preventable diseases and their associated disabilities and premature deaths. To achieve this goal, the science of behavior change increasingly is being recognized as a critical area for research. While NIH historically has invested in biobehavioral research, SOBC is a crucial step to coordinate, leverage, and advance these efforts. The SOBC initiative examines topics that span the continuum of behavior change and across disciplines. The SOBC goals include the identification of new and productive paradigms for SOBC research—paradigms that will facilitate the synthesis, integration, and application of SOBC research; that will help to bridge the distances that often separate investigators and disciplines; and that will inform and identify future research directions and initiatives. On June 15-16, 2009, NIH brought together experts in the fields of basic and applied behavioral sciences, genetics, economics, and methodology with the goal of advancing an NIH-wide agenda on the science of behavior change. The main topics of discussion were the acquisition and prevention of behavior, changing existing behavior, and maintenance of behavior. The SOBC working group will use ideas generated from the meeting to develop new interdisciplinary initiatives in behavior change research.

→ For more information, see http://nihroadmap.nih.gov/documents/SOBC_Meeting_Summary_2009.pdf
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NINR, NIA**, DPCPSI, FIC, NCCAM, NCI, NHGRI, NHLBI, NIAAA, NIAID, NICHD, NIDA, NIDCR, NIDDK, NIGMS, NIMH, NINDS, OBSSR)

Rodent Model Resources for Translational Research: Mouse and rat models are the primary testbed for preclinical research and have played a vital role in most medical advances in the last century. Rodent models comprise about 90 percent of all animal studies, enabling a wide range of genetic and physiological research on human disease. NIH plays a major role in supporting the availability of normal and mutant mice and rats for translational research. Recent accomplishments include:

- *Knockout Mouse Project (KOMP)*—A trans-NIH initiative to individually inactivate approximately 8,500 protein-coding mouse genes to better understand their genetic functions, which are, in many cases, very similar to human genes. High throughput production started in 2006, and international distribution of validated embryonic stem cell lines with specific knockouts from the KOMP Repository became fully operational in 2008. The KOMP is supported by 19 ICs and Offices.
- *Mutant Mouse Regional Resource Centers*—More than 1,700 mutant mouse lines, and 27,000 mutant embryonic cell lines, are available from the consortium, which comprises three centers across the United States.
- *Rat Resource and Research Center*—Acquisition and distribution of rat models increased dramatically in FY 2008, because of adaptation of novel technologies to make directed mutations.

→ For more information, see http://www.genome.gov/17515708
→ For more information, see http://komp.org
→ For more information, see http://www.nih.gov/science/models/mouse/knockout/komp.html
→ For more information, see http://www.mmrrc.org/
→ For more information, see http://www.nrrrc.missouri.edu
→ For more information, see http://www.ncrr.nih.gov/comparative_medicine/resource_directory/rodents.asp
→ This example also appears in Chapter 3: *Genomics*
→ (E) (**NCRR**, NHGRI, NIDA, NINDS)

Biomedical Technology Research Centers (BTRCs): The BTRCs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Centers and through intensive collaborations with other leading laboratories. The BTRCs are used annually by nearly 5,000 scientists

from across the United States and beyond, representing more than $700 million of NIH funding from 22 ICs. As an example, optical technologies enable researchers to:

- Harness the power of light to "see" biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

→ For more information, see http://www.ncrr.nih.gov/biomedical_technology
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NCRR**)

Glycomics Technology Development, Basic Research, and Translation into the Clinic: Glycans are ubiquitous complex carbohydrates found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules is thus critical for basic and clinical research across the spectrum of health and disease, but widely is regarded as one of the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- Biomedical Technology Research Centers develop and share cutting-edge technologies for analysis of carbohydrates in complex biological systems.
- Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.
- Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
- A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.

→ For more information, see http://www.ncrr.nih.gov/glycomics
→ For more information, see http://www.functionalglycomics.org
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NCRR**, NCI, NHLBI, NIGMS, NINDS)

Translational Research at Primate Research Centers: Nonhuman primates are critical components for translational research because of their close physiological similarities to humans. Nonhuman primates widely are used for both hypothesis-based and applied research directly related to human health, such as the development and testing of vaccines and therapies. The NIH-supported National Primate Research Centers (NPRCs) and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using nonhuman primates. NIH support for the centers ensures that these specialized resources are available to the research community. Several NIH ICs provide funding to investigators for specific research projects that use NPRC resources, thus increasing the efficiency of projects involving use of nonhuman primates. For example, in FY 2008, more than 1,000 research projects and more than 2,000 investigators used the animals and other resources provided by the NPRCs. Highlights of research activities include:

- Use of the simian immunodeficiency virus for AIDS-related research, including development and testing of novel microbicides to prevent infection by HIV, the virus that causes AIDS, and testing of AIDS vaccine candidates.
- Identification of the central role of specific genes and molecules in drug addiction and neurological conditions and diseases, studies of the biochemistry and physiology of drug and alcohol addiction, and development of stem cell-based therapies for neurodegenerative diseases.
- Development of the first nonhuman primate model of a neurodegenerative disease-Huntington's disease.

→ Yang SH, et al. *Nature* 2008;452(7197):921-4. PMID: 18488016. PMCID: PMC2652570.
→ For more information, see http://www.ncrr.nih.gov/comparative_medicine/resource_directory/primates.asp
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NCRR**, NIA, NINDS)

Challenge Program in Integrative Research: Mechanisms of Susceptibility to Oxidative-Stress Disease: This project is an interdisciplinary, collaborative effort to combine the use of simple eukaryotic systems, mouse models, genetic polymorphisms, genomics, clinical research, and patient samples to investigate the mechanisms of susceptibility to the development of oxidative stress-induced disease. The initial phase of the program is focused on bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP), chronic diseases associated with very low birth weight infants. This program consists of three interactive projects: (1) positional cloning of BPD/ROP susceptibility genes in inbred mice; (2) investigating the role of mitochondrial reactive oxygen species in hyperoxia-induced tissue injury; and (3) searching for oxidant susceptibility genes and neonatal diseases in prospective case-parent triad cohorts. Together this group will identify stress response networks, develop and validate early biomarkers of disease, and identify candidate genes and genetic polymorphisms that influence susceptibility to oxidative stress. This program has established a highly collaborative research team uniting bench science with clinical research and patient outcomes. The long-term goal of this program is to understand the role of specific genes that increase human susceptibility to oxidant stress-induced diseases. Thus, this team has the potential to affect a large number of environmentally induced diseases associated with inflammation and reactive oxygen species, including asthma, atherosclerosis, cancer, cardiovascular disorders, and neurodegenerative diseases.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
→ (I) (**NIEHS**)

Stem Cells and Regenerative Medicine: Stem cells are able to renew themselves and generate progeny that differentiate into more specialized cells. They play critical roles in organism development, and some are essential for normal homeostasis and tissue repair. NIH has made a significant investment in stem cell research. One NIH-supported study showed that the sex of cells in a subpopulation of muscle-generating stem cells in adult mice can influence their capacity to repair tissue considerably. This finding could lead to future therapies for various diseases, including muscular dystrophy. A collaboration between NIH Intramural researchers and those at Walter Reed Army Medical Center discovered that waste tissues from surgery, removed to promote healing of orthopaedic injuries and war-traumatized muscle, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells. They could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest cells. NIH has partnered with the Department of Defense on an initiative to speed treatments to wounded soldiers abroad, and civilian trauma victims and burn patients in the United States. This collaboration has resulted in the establishment of the new Armed Forces Institute of Regenerative Medicine (AFIRM). The AFIRM-led program will focus on regrowing fingers, repairing shattered bones, and restoring skin to burn victims with genetically matched skin, to pave the way for commercial products in the near future. Hair follicles are useful models for organ regeneration. Recent discoveries have been made in the molecular processes that govern the growth of hair follicle stem cells, which are a source for newly formed hair follicles.

→ Deasy BM, et al. *J Cell Biol* 2007 Apr 9;177(1):73-86. PMID: 17420291. PMCID: PMC2064113.
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Nesti LJ, et al. *J Bone Joint Surg Am* 2008;90(11):2390-8. PMID: 18978407. PMCID: PMC2657299.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cell_sex_and_stem_cell.asp
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/progenitor_cells.asp
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E/I) (**NIAMS**, NIA, NIAID, NIBIB)

Bisphenol A Exposure and Effects: More than 90 percent of the U.S. population is exposed to low levels of BPA. Exposures may occur through use of polycarbonate drinking bottles and the resins used to line food cans. The NIH National Toxicology Program's (NTP's) Center for the Evaluation of Risks to Human Reproduction conducted an evaluation to determine whether current levels of exposure to BPA present a hazard for human reproduction and/or development. Following this evaluation of existing literature, the NTP expressed "some concern" for effects on the brain, behavior, and prostate gland based on developmental effects reported in some laboratory animal studies using BPA exposures similar to those experienced by humans. NIH is working to address and support research and testing needs identified during the NTP evaluation to understand any potential risks for humans from BPA exposure. In collaboration with scientists at the FDA National Center for Toxicological Research, the NTP has designed and begun studies to evaluate similarities and differences in how rats metabolize BPA in relation to nonhuman primates, and to further understand the long-term health consequences from exposures to low levels of BPA during rodent development. In addition, NIH is providing grant support to the extramural community for studies that focus on investigating possible long-term health outcomes from developmental exposure or chronic exposures to environmentally relevant doses of BPA. Collectively, these studies should address research gaps, reduce uncertainties, and provide perspective regarding any potential risk that BPA poses for public health.

→ Mahalingaiah S, et al. *Environ Health Perspect* 2008;116(2):173-8. PMID: 18288314. PMCID: PMC2235217.
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→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
→ (I) (**NIEHS**)

Experimental Therapeutics for Cancer: The NCI Experimental Therapeutics Program (NExT) is an integrated drug discovery and development effort that concentrates research into a single robust pipeline that starts with discovery of promising compounds and leads, through a series of progressive steps, to first-in-human studies. The ultimate goal is to accelerate the translation of new oncology agents to the clinic.

→ For more information, see http://dctd.cancer.gov/About/major_initiatives_NExt.htm
→ This example also appears in Chapter 2: *Cancer*
→ (E/I) (**NCI**)

Alzheimer's Disease Neuroimaging Initiative (ADNI): ADNI is an innovative public-private partnership for examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease (AD). ADNI has reached its target enrollment of 800 participants, and supported development of a number of tools and methods now in use in the United States as well as in Japan, the European Union, and Australia. Other expansions include a genome-wide association study of ADNI participants scheduled to provide the most extensive and robust dataset of its kind in the AD field; a study that allows for longitudinal analysis by the collection of additional cerebrospinal fluid from participants over several years; and a study exploring the use of PET and Pittsburgh Compound B (PIB) as a tool for developing biochemical markers. A recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer's and established a method and standard of testing for these biomarkers.

→ For more information, see http://www.loni.ucla.edu/ADNI
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIA**, NIBIB)

Therapeutics for Rare and Neglected Diseases Program (TRND): NIH is developing a congressionally mandated therapeutics development program for rare and neglected diseases. The ORDR will handle oversight and governance of TRND, and researchers will perform TRND's laboratory work in a new facility administered by the intramural program of NHGRI. TRND will build upon the similarly structured NIH Chemical Genomics Center (NCGC). NCGC facilitates drug development from the basic research laboratory to the chemical probe stage, which is when researchers begin to lay the groundwork for intensive preclinical development of candidate drugs. Picking up where NCGC and other organizations leave off, TRND will concentrate its efforts on the preclinical stage of drug development. TRND's aim will be to move candidate drugs forward in the drug development pipeline until they meet Food and Drug Administration (FDA) requirements for an Investigational New Drug (IND) application. Once TRND generates enough data to support an IND application for a candidate drug, it will be licensed to an experienced organization outside of NIH, such as a biotechnology or pharmaceutical company, for human testing and regulatory submission. TRND also will devote considerable resources to the repositioning or repurposing of approved products for use in rare and neglected diseases. Like NCGC, TRND will pull together researchers with expertise in a broad and diverse range of scientific disciplines and disease areas. Specifically, TRND will encourage investigators from both inside and outside of NIH, from the public, private, and nonprofit sectors, to submit projects for work within its intramural facility. This will create ongoing collaborations that will benefit researchers and, most importantly, patients with rare and neglected diseases. NIH ICs and Offices have recommended staff members with expertise and experiences in product development programs to serve on a Trans-NIH Staff Advisory Group that will provide ongoing consultation regarding the operation of TRND and help integrate TRND with related or complementary efforts in the NIH ICs. A second group providing input for TRND is the External Expert Panel comprised of experts in preclinical drug development and rare and neglected diseases from academia, industry, and patient advocacy communities.

→ For more information, see http://www.genome.gov/27531965
→ For more information, see https://rarediseases.info.nih.gov/TRND/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E/I) (**ODP/ORDR**, NHGRI)

Neurobiology of Pain in Sickle Cell Disease: The past 35 years have produced a remarkable expansion in scientific understanding of the neurobiological basis of pain, yet none of this research has been specifically focused on sickle cell disease (SCD), one of the few human diseases associated with lifelong, often severe, pain. To address this gap, an NIH-sponsored working group brought together researchers studying the neuroscience of pain and hematologists having a special interest in SCD. Participants identified an urgent need for multidisciplinary studies encompassing neurobiology, hematology, pharmacology, and psychology. Based on the working group findings, in November 2008, NIH issued a request for grant applications, Exploratory Studies in the Neurobiology of Pain in Sickle Cell Disease, to support basic and translational studies on the distinctive aspects of pain syndromes in SCD.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-008.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NHLBI**, NINDS)

NIH Guidelines on Ethical Issues Associated with Human Specimen and/or Data Collections: Human specimen and/or data collections increasingly are important for advancing basic biomedical and behavioral research and translating discoveries into improved health care. While numerous regulations and policies apply to specimen and data research, there is no comprehensive Federal policy that covers the full spectrum of activities involved with collection, storage, sharing, distribution, and use of human specimens and/or data for research. To address this need, NIH is developing draft guidelines for human specimen and data collections conducted or supported by NIH. The guidelines address ethical issues, including informed consent, protection from research risks, withdrawal of specimens and data, as well as management, oversight, access, and dissemination. The draft guidelines are expected to be issued for public comment in late 2009.

→ For more information, see http://oba.od.nih.gov/policy/policy_issues.html#CRP_004
→ (O) (**OSP/OBA**)

Molecular Profiling to Tailor Cancer Treatment: Molecular profiling is a powerful tool for identifying tumor subtypes and guiding clinical decisions to optimize patient benefit. NIH programs in this area include the Strategic Partnering to Evaluate Cancer Signatures (SPECS) Program, which is evaluating the clinical utility of molecular signatures and helping translate molecular data into improved patient management, and the Lymphoma/Leukemia Molecular Profiling Project. Several studies from these and other programs demonstrate the value of tailoring cancer treatment based on molecular characteristics of the patient and tumor. Gene expression profiling revealed distinct diffuse large B-cell lymphoma (DLBCL) subtypes, one of which exhibits activation of the pro-survival NF-κB pathway. A recent study confirmed that bortezomib, a drug that indirectly prevents NF-κB activation through proteasome inhibition, selectively enhances the effects of chemotherapy in this DLBCL subtype. A recent study revealed that head and neck squamous cell carcinomas (HNSCCs) associated with human papilloma virus (HPV)-16 are more responsive to treatment than HPV-negative HNSCCs. Results from a recent clinical trial indicate that advanced colorectal cancers should be tested for mutations in the KRAS gene. Patients with tumors housing KRAS mutations are unlikely to benefit from targeted therapies that block epidermal growth factor receptor activity and should thus be spared the side effects and costs associated with these drugs. SPECS researchers recently developed an assay to classify breast cancer molecular subtypes and showed that when used in combination with clinicopathologic parameters (e.g., stage, grade), the assay improved prediction of prognosis and chemotherapy benefit.

→ Dunleavy K, et al. *Blood* 2009;113(24):6069-76. PMID: 19380866. PMCID: PMC2699229.
Fakhry C, et al. *J Natl Cancer Institute* 2008;100(4):261-9. PMID: 18270337.
Walther A, et al. *Nat Rev Cancer* 2009;9(7):489-99. PMID: 19536109.
Parker JS, et al. *J Clin Oncol* 2009;27(8):1160-7. PMID: 19204204. PMCID: PMC2667820.
→ For more information, see http://www.cancerdiagnosis.nci.nih.gov/specs/index.htm
→ For more information, see http://llmpp.nih.gov
→ (E/I) (**NCI**)

Nanotechnology in Cancer: Nanotechnology innovation has been driven predominantly by physicists, engineers, and chemists; progress in cancer research comes primarily from discoveries of biologists and oncologists. The NIH Alliance for Nanotechnology in Cancer has set a goal of creating a community of cancer nanotechnologists who work together to develop nanotechnology approaches; apply them to the prevention, diagnosis, and treatment of cancer; and educate the medical community about opportunities enabled by cancer nanotechnology. The Alliance organized a session at 2009 American Association for Cancer Research meeting on Cancer Diagnostics Using Nanotechnology Platforms. Participants included high-profile investigators who work on the development of new nanodevices for in vitro diagnosis and in vivo imaging and clinicians who define oncology applications of those devices. Examples of this work include: PRINT, a technique allowing for controllable fabrication of nanoparticles; researching novel diagnostic techniques for proteins and DNA; developing implantable nanosensors; researching novel nanoparticle-based imaging agents and nanosensors; and developing nanotechnology-based cancer screening tools.

→ For more information, see http://nano.cancer.gov/
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*
→ (E/I) (**NCI**)

NIH Bench-to-Bedside Program: An intramural Bench-to-Bedside Program was established in 1999 to integrate the work of basic and clinical scientists on the NIH campus and to foster collaborations across Institutes. Since the program's beginning, more than 500 principal and associate investigators have collaborated on 152 funded projects with approximately $33 million distributed in total bench-to-bedside funding. The program scope broadened in 2006 to include partnerships between intramural and extramural programs as part of a broader NIH effort to reduce barriers between intramural and extramural communities. Four funding cycles have been completed successfully, with approximately 50 extramural institutions partnering on bench-to-bedside awards (15 of these are CTSA sites). Last year the program expanded to allow extramural investigators to initiate bench-to-bedside awards. The call for proposals invited extramural investigators to identify intramural partners to lead the study via the CTSA network. As NIH explores opportunities to promote expanded collaborations with extramural clinical researchers, governing entities are exploring stable funding for the Bench-to-Bedside Program. Also under consideration is the establishment of a grants-type mechanism for bench-to-bedside awards that would allow direct funding to intramural and extramural investigators and streamline funds distribution. This program has served as a successful model of an intramural initiative that has broadened to include extramural partnerships.

→ For more information, see http://clinicalcenter.nih.gov/ccc/btb/awards.shtml
→ (E/I) (**CC**, NCMHD, NCRR, OAR, OBSSR, ODP/ORDR, ORWH)

Clinical Research: Learning Which Interventions Work

Recovery After an Initial Schizophrenic Episode (RAISE): Significant impairment of social and vocational function is the norm in chronic schizophrenia, and while antipsychotic drugs remain effective, they are not able to restore skills and abilities lost to the illness. A person experiencing an initial psychotic episode usually responds well to antipsychotics and, unlike chronically ill patients, may recover completely from that first episode. NIH will fund an initiative to determine

whether function could be preserved and disability forestalled after an initial schizophrenic episode with an intense and sustained pharmacological, psychosocial, and rehabilitative intervention. A single project will be supported to: (1) test the feasibility of recruiting and retaining newly diagnosed patients in a longitudinal trial; (2) develop the treatment model—a mix of pharmacological, psychological, and rehabilitative interventions—that is most likely to preserve function and maintain patient participation; and (3) determine the nature of the control intervention. This initiative will set the stage for a large-scale, definitive, randomized clinical trial.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIMH**) (ARRA)

Clinical Trials Networks for the Treatment of Mental Disorders: NIH is using its extensive clinical trials networks as platforms for investigating effective treatments for mental disorders. The networks, which are maintained through infrastructure supported by NIH, evolved from a recent series of practical clinical trials. The networks comprise more than 60 sites throughout the United States that maintain continual outreach efforts to diverse groups of patients and families with mental illnesses. The Bipolar Trials Network is conducting the Lithium Use for Bipolar Disorder (LiTMUS) trial, which will study the use of moderate-dose lithium for the treatment of bipolar disorder among 264 participants. The Depression Trials Network is seeking participants for the Combining Medications to Enhance Depression Outcomes (CO-MED) trial. This study will examine for the first time whether two different medications, when given in combination as the first treatment step, compared to one medication, will enhance remission rates, increase speed of remission, be tolerable to the participant, and provide better sustained benefits in the longer term. Results of this study, involving 660 participants, will inform practitioners in managing the treatment of patients with chronic or recurrent depression.

→ For more information, see http://www.clinicaltrials.gov/show/NCT00667745
→ For more information, see http://www.clinicaltrials.gov/show/NCT00590863
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIMH**)

Advances in Mental Health Treatment Development: NIH continues to fund research into the development of targeted medications and treatments for mental disorders.

- *Novel NeuroAIDS Therapies:* Integrated Preclinical/Clinical Program (IPCP): The IPCP supports drug development efforts focused on new targets that may modulate immune responses and protect brain cells in the context of HIV infection. One NIH-supported group will develop the use of nanotechnology to enhance delivery of HIV drugs to the brain. Another research group will investigate the therapeutic potential of various compounds to treat or prevent HIV-associated mental disorders.
- *Innovative Approaches to Personalizing the Treatment of Depression:* NIH will advance research on individualizing the treatment of depression by supporting efforts to develop models and test new approaches that, by accounting for patient characteristics, aim to be more specific and thus potentially lead to more effective and efficient treatment interventions. Several studies will be supported through this initiative.
- *Fast-acting Depression Treatments:* Previous NIH-funded research found that ketamine can lift depression in just hours, instead of the weeks it takes conventional antidepressants. NIH researchers now have identified a marker that predicts a patient's response using the split-second accuracy of magentoencephalography. Depressed patients showed increased activity in the anterior cingulate cortex (ACC; a region found in brain imaging studies to signal better treatment responsiveness) that correlated with their response to ketamine while viewing certain visual stimuli. This ACC activity may indicate the dysfunctional workings of the brain circuit that is targeted by ketamine.

→ Salvadore G, et al. *Biol Psychiatry* 2009;65(4):289-95. PMID: 18822408. PMCID: PMC2643469.
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-040.html

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-010.html
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E/I) (**NIMH**)

Functional Gastrointestinal (GI) Disorders: NIH is leading a number of initiatives to improve the diagnosis and treatment of functional GI disorders. The Gastroparesis Clinical Research Consortium (GpCRC) performs clinical, epidemiological, and therapeutic research to improve treatment of patients with gastroparesis (inability to move food properly from the stomach through the digestive system). Ongoing GpCRC studies include the Gastroparesis Registry and a multicenter, randomized clinical trial testing the use of nortriptyline (a tricyclic antidepressant) for treatment of gastroparesis. The use of antidepressants for the treatment of functional dyspepsia (indigestion) is being tested in the Functional Dyspepsia Treatment Trial; the study also aims to identify genetic markers associated with improved treatment outcomes. Additional NIH-sponsored clinical studies are testing the benefit of short-term cognitive-behavioral treatment for irritable bowel syndrome (IBS) and evaluating methods for diagnosing and treating Sphincter of Oddi Dysfunction, a disorder that results in bouts of abdominal pain from spasms of biliary and pancreatic valves. In addition, NIH provides continued support for the Center for Neurovisceral Sciences and Women's Health at UCLA, which conducts basic and clinical research on how the brain and digestive system communicate and how alterations in this communication result in IBS and other disorders. These initiatives will reduce the physical and psychosocial burdens associated with functional GI disorders.

→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00398801
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00765895
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00248651
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00738920
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00688662
→ For more information, see http://www.cns.med.ucla.edu
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDDK**, NCCAM, ORWH)

Phase II Clinical Trials of Novel Therapies for Lung Diseases: Better treatments and diagnostic procedures are needed for lung diseases and sleep disorders. Although the results of basic research studies in cells, tissues, and animal models; investigations of biomarkers; and functional genomics have improved understanding of the pathogenesis of lung diseases and sleep disorders and suggested treatment targets, human testing often has not kept pace with the basic science advances. A recent solicitation encourages Phase II clinical trials to provide high-quality, proof-of-concept data to justify larger clinical efficacy trials. To foster collaborations between basic and clinical researchers and to obtain mechanistic understanding of new treatment approaches, each project is to include one interventional clinical trial led by a clinical investigator and at least one basic ancillary research study that is tightly related to the clinical question and led by a basic researcher. It is expected that four to six awards will be made in FYs 2010 and 2011.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-003.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NHLBI**)

Obstructive Sleep Apnea Treatment Trials: In 2009, NIH completed two prospective, randomized, double-blinded, sham-controlled multicenter evaluations of nasal continuous positive airway pressure (CPAP) as a first-line treatment for obstructive sleep apnea (OSA). OSA is characterized by brief episodes of airway obstruction that prevents air from reaching the lung and disturbs sleep. It is the single most pervasive airway disorder and is associated with a greater risk of behavioral impairment, hypertension, stroke, diabetes, and all-cause mortality. The $14 million Apnea Positive Pressure

Long-Term Efficacy Study (APPLES) was launched in September 2002 to determine whether CPAP therapy, compared with placebo, alleviates debilitating cognitive impairment associated with OSA. More than 1,100 OSA cases were studied over a period of 6 months using a battery of behavioral and sleep tests to assess changes in cognitive ability, mood, sleepiness, and quality of life. The $3 million CATNAP study was launched in August 2003 to assess the threshold of OSA severity at which CPAP therapy improves sleep-related functional and medical outcomes. It studied 200 cases of mild OSA in which participants exhibited significant sleepiness. Findings from APPLES and CATNAP that are to be reported in 2010 will be the first evidence from U.S.-based clinical trials to guide health care providers in determining who should be evaluated and treated and what behavioral benefits can be expected.

→ Kushida CA, et al. *J Clin Sleep Med* 2006;2(3):288-300. PMID: 17561541.
Saboisky JP, *Expert Opin Ther Targets* 2009;13(7):795-809. PMID: 19530985. PMCID: PMC2729816.
Calvin AD, et al. *Metab Syndr Relat Disord.* 2009;7(4):271-8. PMID: 19344228.
→ For more information, see https://apples.stanford.edu
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NHLBI**)

The Osteoarthritis Initiative: A limited number of therapies exist for osteoarthritis (OA) treatment. Most only relieve pain and reduce disability; none slows or halts disease progression. One barrier to the development of drugs that block the underlying causes of OA symptoms is the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. To overcome this problem, NIH—with input from FDA—partnered with private sponsors to create the Osteoarthritis Initiative (OAI). When complete, the OAI will provide an unparalleled state-of-the-art database showing both the natural progression of the disease and information on risk factors, joint changes, and outcome measures. All data will be freely available to researchers worldwide, who can develop hypotheses about possible OA biomarkers of disease onset and progression, test their theories, describe the natural history of OA, and investigate factors that influence disease development and severity. Scientists also can use the OAI to identify potential disease targets and to develop tools for measuring clinically meaningful improvements. The OAI originally was to receive funding through FY 2009, during which time investigators would collect survey, clinical, and image data and biological samples from approximately 4,800 people at baseline, 12-, 24-, 36-, and 48-month time points. NIH extended the study to include 72- and 96-month data. By the end of FY 2009, more than 1,350 researchers from 54 countries had registered to access OAI data. A total of 4,100 clinical datasets have been downloaded. In FYs 2008 and 2009, more than 18 articles using OAI data were accepted for publication in peer-reviewed journals.

→ For more information, see http://www.niams.nih.gov/Funding/Funded_Research/Osteoarthritis_Initiative
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIAMS**, NCCAM, NCMHD, NIA, NIBIB, NIDCR, ORWH) (GPRA)

Progress Toward Immune Tolerance: Since 1999, NIH, with its cosponsor the Juvenile Diabetes Research Foundation International, has supported the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. The ITN is pioneering novel strategies for studying and testing new drugs and therapies against autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based upon principles of immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to "reeducate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. To understand the underlying mechanisms of action of the candidate therapies and to monitor tolerance, the ITN has established state-of-the art core laboratory facilities to conduct integrated mechanistic studies, and to develop and evaluate markers and assays to measure the induction, maintenance, and loss of tolerance in humans. Current ITN studies include pancreatic islet transplantation for type 1 diabetes; approaches to slow or reverse progression of autoimmune diseases such as type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus and other rheumatologic disorders; approaches to

treat and prevent asthma and allergic disorders, including food allergy; and therapies to prevent liver and kidney transplant rejection without using lifelong immunosuppressive drugs.

→ For more information, see http://www.immunetolerance.org/
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIAID**, NIDDK)

Transforming TB Research: Diagnosis, treatment, and control of tuberculosis (TB) increasingly are complicated by the HIV/AIDS co-epidemic and the emergence of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR TB). NIH is pursuing six critical areas for additional investigation: (1) new TB diagnostic tools; (2) improved therapies for all forms of TB; (3) basic biology and immunology of TB; (4) MDR TB and XDR TB epidemiology; (5) clinical management of MDR TB and XDR TB in people with and without HIV infection, including children; and (6) TB prevention, including vaccines. Recent NIH advances in TB research include:

- Two FDA-approved drugs are found to work in tandem to kill laboratory models of *Mycobacterium tuberculosis* (Mtb) strains, the bacterium that causes TB. The drugs—meropenem and clavulanate—are used to treat other bacterial diseases. A clinical trial is being developed to test the combination in people who have XDR TB.
- New information on the pharmacology of existing and new anti-TB compounds may facilitate the development of improved treatment regimens for adults and children.
- Clinical trials have shown that the immune systems of children who are HIV-infected do not respond well to the current TB vaccine, BCG.
- Clinical trials also have shown that mortality among TB patients coinfected with HIV is reduced drastically when antiretroviral therapy is provided at the same time as TB therapy. Additional studies are underway to determine optimal strategies for the prevention, treatment, and diagnosis of TB in the setting of HIV infection.

Several NIH-supported academic institutions, public-private partnerships, and commercial entities are developing rapid tests for early detection of all forms of TB, including MDR and XDR TB.

→ For more information, see http://www3.niaid.nih.gov/topics/tuberculosis
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E/I) (**NIAID**)

Preventing Drug Abuse in Children and Adolescents: Intervening early to reduce risk factors for drug abuse and related problem behaviors can have tremendous impact and improve the trajectory of a young life. NIH is using a multipronged approach to achieve more effective substance abuse prevention by: (1) developing novel strategies, (2) exploring long-term and crossover effects of proven programs, and (3) improving adoption and implementation of evidence-based approaches. Innovative ideas being explored include physical activity to counter drug use, interactive Web-based technologies to engage young people, and brain imaging results to better target media messages. NIH also is building on proven methods such as universal prevention programs, which can reduce an array of risk behaviors, including substance abuse. These programs typically target behaviors appropriate to a child's developmental stage and have been shown to achieve long-term effects. For example, fifth graders who participated in the school-based prevention program "Positive Action" as first graders were about half as likely to engage in substance abuse, violent behavior, or sexual activity as those who did not. Similarly, exposure to the "Good Behavior Game," designed to reduce aggressive, disruptive behavior in first and second grade classrooms, led to fewer drug and alcohol disorders, lower rates of regular smoking, less antisocial personality disorder, and reduced delinquency and violent crime in young adults. However, the development of evidence-based prevention programs is meaningless unless they are adopted by communities. Therefore, NIH also is striving to increase implementation of successful prevention approaches in U.S. schools and communities.

→ Beets MW, et al. *Am J Public Health* 2009;99(8):1-8. PMID: 19542037.
Kellam SG, et al. *Drug Alcohol Depend* 2008;95 Suppl 1:S5-S28. PMID: 18343607. PMCID: PMC2512256.
Spoth R, et al. *Am J Prev Med* 2007;32 (5):395-402. PMID: 17478265.
→ For more information, see http://www.nida.nih.gov/scienceofaddiction/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIDA**)

Comorbidity: Addiction and Other Mental Disorders: Drug addiction frequently is accompanied by other psychiatric diseases, which can complicate its diagnosis and treatment. Thus, NIH supports research on the multiple facets of psychiatric comorbidity across multiple health sectors. This approach explores whether drug use leads to mental illness or the reverse, what causes their frequent co-occurrence (e.g., shared genetic and environmental vulnerabilities or similarities in brain circuits and chemical messengers), and how to treat both comprehensively. Specific activities include epidemiological research on mental health/drug abuse comorbidity, such as secondary analyses of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study and the National Comorbidity Survey to better understand the prevalence and variety of comorbidities, and clinical trials to help assess the actions of combined or dually effective behavioral and medication treatments (e.g., in adolescent and adult patients with attention deficit/hyperactivity disorder [ADHD] and substance abuse problems). It also includes a push for research to investigate drug abuse and mental health screening for all those entering the criminal justice system, a notable gap, particularly for adolescents. Another identified gap calls for research using preclinical models of comorbidity to explore the neurological bases of comorbid drug abuse and other mental illness (e.g., overlapping circuitry). Joint requests for applications issued by multiple ICs have elicited studies examining everything from the role of depression and anxiety in the tobacco epidemic to the neural bases of ADHD in fetal drug or alcohol exposure to improving care for co-occurring disorders in rural areas via new technologies. (Note: NESARC and the National Comorbidity Survey are nationally representative surveys in the United States that assess the prevalences and correlates of DSM-III-R disorders, including substance use and mental health disorders.)

→ For more information, see http://www.drugabuse.gov/CTN/protocol/0028.html
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0029.html
→ For more information, see http://www.nida.nih.gov/ResearchReports/comorbidity
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDA**, NIAAA, NIMH)

The Critical Need for Addiction Medications: Breakthrough discoveries in the last decade have led to a profound transformation in understanding the mechanisms and consequences of drug abuse and addiction. The current picture offers a unique opportunity for the results of NIH's collective research to be translated into new, effective pharmacotherapies that could, either by themselves or with tested behavioral treatments, help alleviate the devastating personal and societal impacts of addiction. Distinct from the process that occurs with many other diseases, medications development for addiction suffers from minimal pharmaceutical industry involvement—likely because of real or perceived financial disincentives and stigma. Thus, despite many enticing scientific leads, we still have no medications available for stimulant, cannabis, inhalants, or polysubstance abuse, a gap that NIH is attempting to fill. Current efforts are capitalizing on a greater understanding of the neurobiology underlying addiction and of newly identified candidate systems and molecules. Several innovative treatment approaches—beyond targeting the brain's reward system—have proven feasible and are progressing to more advanced stages of research and development. Projects in this context include work on medications to diminish conditioned responses, promote new learning, and inhibit stress-induced relapse. In addition, vaccines (e.g., for nicotine, cocaine) are being developed that induce the body to produce drug-specific antibodies able to sequester drug molecules while they are still in the bloodstream and prevent them from entering the brain. Next-generation

pharmaceuticals also will emerge from human genome studies uncovering novel targets for better tailoring of treatments according to a person's genes.

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDA**) (GPRA)

Comparative Effectiveness of Treatments for Common Childhood Eye Disorder: Convergence insufficiency (CI) is a relatively common vision problem that develops in childhood in which the eyes do not naturally turn inward when focusing on a close-up visual target. Symptoms include eye strain, blurred vision, headaches, and discomfort. CI can adversely affect reading ability and reading comprehension and can have a serious impact on an individual's performance in school, career, and quality of life. Eye care professionals treat CI with various forms of eye exercises, done at home or in the office of a trained therapist, that require children to sustain focus on nearby objects. The Convergence Insufficiency Treatment Trial (CITT) compared the effectiveness of these therapies. Results indicate that the most popular treatment, known as home-based pencil push-up therapy, was no more effective in improving patient's symptoms than a placebo therapy. However, 73 percent of children assigned to a regimen of intensive, office-based therapy combined with home reinforcement did improve significantly compared to the placebo group. Other commonly prescribed home-based regimens also showed some benefit but were only about half as successful as office-based therapy with home reinforcement. Although home-based treatments for CI are appealing because of their simplicity and low cost, these results indicate that office-based treatment combined with home reinforcement is more effective in helping children to achieve normal vision and reducing symptoms.

→ Convergence Insufficiency Treatment Trial Study Group. *Arch Ophthalmol* 2008;126(10):1336-49. PMID: 18852411. PMCID: PMC2779032.
→ For more information, see http://archopht.ama-assn.org/cgi/content/full/126/10/1336
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NEI**)

NIH Establishes Neuro-Ophthalmology Clinical Research Network: The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) Network was established in spring of 2009 to investigate disorders that bridge neurology and ophthalmology and that often are difficult to diagnose and treat. The Network involves more than 200 community and academic practitioners. This consortium will provide a unique opportunity to recruit and study hard-to-find patients to evaluate risks, diagnoses, and treatment options that could not be accomplished without a coordinated effort. The first clinical trial funded under this network will be the Idiopathic Intracranial Hypertension (IIH) Treatment Trial. IIH typically occurs in women of childbearing age. Obesity increases the risk 20-fold. IIH is characterized by an increase in intracranial pressure resulting in blurred vision, double vision, and permanent vision loss. This trial will compare the additional benefit of acetazolamide (a diuretic) added to a low-sodium, weight reduction diet in newly diagnosed patients. Future planned studies include comparing treatments for ocular manifestations in Graves' disease, an autoimmune disorder that causes hyperthyroidism, estimated to affect 2 percent of all women between the ages of 20 and 40. Patients with Graves' can develop protrusion of the eye balls and optic nerve damage. A network of researchers provides valuable expertise and widespread recruitment capabilities for studies of rare disorders.

→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E) (**NEI**)

Comparative Effectiveness Study Finds Laser Treatment Preferable in Diabetic Macular Edema: The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network dedicated to conducting multicenter clinical research for diabetic retinopathy and associated conditions. The DRCR.net was formed in September 2002 and currently includes 199 participating sites with more than 670 physicians throughout the United States. About 45 percent of the 18 million Americans diagnosed with diabetes have visual disorders such as macular edema. This occurs when the central part of the retina called the macula swells in diabetics—possibly leading to blindness. Laser treatment to reduce swelling has been the standard of care. However, early reports of success in treating diabetic macular edema with a corticosteroid, triamcinolone, have led to its widespread use. A DRCR clinical trial found that laser therapy is more effective and has far fewer side effects than intraocular injections of triamcinolone in treating diabetic macular edema. In the corticosteroid-treated group, 28 percent experienced substantial vision loss as compared to 19 percent in the laser-treated group. Surprisingly and unexpectedly, vision improved in about one-third of the eyes treated with laser therapy. Results of this study confirm the preferential use of laser treatment for diabetic macular edema.

→ Diabetic Retinopathy Clinical Research Network, et al. *Ophthalmology* 2007;114(10):1860-7. PMID: 17698196. PMCID: PMC2245885.
→ For more information, see http://public.drcr.net/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NEI**)

Progress in Parkinson's Disease Research: For the past 7 years, NIH actively has been engaged in identifying gaps in Parkinson's disease research and developing programs to address them. Examples of progress include initiation of Phase III clinical trials of creatine and coenzyme Q10 to treat early Parkinson's disease; development of diagnostic criteria for depression and psychosis in people with Parkinson's disease; and support for a Parkinson's disease Gene Therapy Study Group. In 2009, a major clinical trial cofunded by NIH and the Veterans Administration published its finding that Deep Brain Stimulation is more effective than standard drug therapy for Parkinson's disease but also carries a higher risk of adverse events. NIH also has begun to formally assess the effectiveness of its programs by completing an evaluation of its Morris K. Udall Centers of Excellence in Parkinson's Disease Research. This evaluation included an assessment of scientific progress made by the centers and the value of using a centers mechanism, as well as an exploration of the effectiveness of program management and review in supporting the centers. The Working Group tasked with this evaluation released its findings in September 2007.

→ Weaver FM, et al. *JAMA* 2009;301(1):63-73. PMID: 19126811.
→ For more information, see http://www.ninds.nih.gov/funding/research/parkinsonsweb/index.htm
→ For more information, see http://www.parkinsontrial.ninds.nih.gov/index.htm
→ For more information, see http://www.ninds.nih.gov/news_and_events/press_releases/pressrelease_creatine_03222007.htm
→ For more information, see http://www.ninds.nih.gov/udall_centers_evaluation
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E) (**NINDS**)

Clinical Research and Trials in Neurological Disease: NINDS funds more than 1,000 extramural clinical research studies. Clinical researchers are studying, for example, disease mechanisms, risk factors that contribute to health disparities, brain imaging, and genes that predispose to disease as well as conducting multisite clinical trials that test the safety and efficacy of new prevention strategies and treatments or compare existing interventions. In the past year, for example, an NICHD/NINDS clinical trial reported that a drug commonly used to delay labor can prevent cerebral palsy in some circumstances, and a Veterans Administration/NINDS trial demonstrated that deep brain stimulation, a surgical intervention, is more effective than drug treatment at improving movement and quality of life for many people who have Parkinson's disease, but carries some risks. Among trials now underway, researchers are testing interventions to protect the

brain following traumatic brain injury, to prevent stroke, to slow the progression of neurodegenerative diseases, and to treat multiple sclerosis. An independent study contracted by NINDS found that NINDS clinical trials which cost $335 million over 10 years provided benefits that exceeded $15 billion and added 470,000 healthy years of life to people in the United States. With guidance from an expert strategic planning panel, NINDS is continuing to improve the efficiency and payoff of the clinical trials program.

→ Johnston SC, et al. *Lancet* 2006;367:1319-27. PMID: 16631910.
Weaver FM, et al. *JAMA* 2009;301(1):63-73. PMID: 19126811.
Rouse DJ, et al. *N Engl J Med* 2008;359(9):895-905. PMID: 18753646.
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E) (**NINDS**, NICHD)

Research on Rare Neurological Disorders: NIH supports research to uncover the causes of and develop treatments for the hundreds of rare disorders that affect the nervous system, while also promoting research on topics such as stem cells, gene therapy, and neuroimaging that will impact multiple rare disorders. NIH reissued a Funding Opportunity Announcement (FOA) for new and renewal applications to continue the Rare Diseases Clinical Research Network (RDCRN), which funds collaborative clinical research consortia focused on rare diseases. NINDS will oversee the network's Data Management and Coordinating Center, and several of the consortia to be funded through this program focus on neurological disorders, including dystonia, brain vascular malformations, lysosomal storage disorders, and rare diseases of the autonomic nervous system. Through the NINDS translational research program, NIH supports milestone-driven therapy development for rare neurological diseases. Two funded projects, in Batten disease and Niemann-Pick disease, are nearing investigational new drug approval from FDA to conduct clinical trials, and a newly awarded project focuses on gene therapy approaches for the lysosomal storage disorders Tay-Sachs, San Fillipo, and Sandhoff disease. NIH also continues to support and encourage research to understand and treat Ataxia-telangiectasia and dystonia (including rare dystonias) through separate FOAs issued in collaboration with patient organizations.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-272.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-397.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-08-001.html
→ For more information, see http://www.ninds.nih.gov/research/translational/Coop_Tran_Res.htm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E) (**NINDS**, NCI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NICHD, NIDCD, NIDCR, NIDDK, NIEHS, NINR, ODP/ORDR)

Specialized Program of Translational Research in Acute Stroke (SPOTRIAS): The objective of the SPOTRIAS is to serve as an incubator for translational and early-phase clinical research studies. SPOTRIAS sites are located at medical centers where staff have the capacity to evaluate and treat stroke patients very rapidly after symptom onset. NIH supports eight SPOTRIAS sites that have made substantial progress, including impressive increases in tPA use; the establishment of three interlinked repositories for protein and DNA tissue samples, neuroimages, and clinical data; enrollment of more than 951 individuals with acute stroke into treatment protocols; the management of 20 early-phase clinical trials; and the training of 79 research fellows.

→ For more information, see http://www.spotrias.com
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E, I) (**NINDS**)

Clarification of Optimal Anticoagulation Through Genetics (COAG): NIH has launched the COAG trial to gain a better understanding of the influences of clinical and genetic characteristics of patients in determining a safe and optimal dose of the drug warfarin. The most commonly used oral anticoagulant in the United States, warfarin is used to prevent dangerous blood clots that can potentially lead to pulmonary emboli and strokes. The drug is challenging for doctors to prescribe because the ideal dosage can vary widely from one person to another. Getting the wrong amount of warfarin can be dangerous—if the dose is too high, patients could bleed profusely; if too low, life-threatening clots could develop. The COAG study will determine whether knowledge about some specific genes will help physicians find the safest, most effective warfarin dose for their patients. The prospective, multicenter, randomized clinical trial will recruit more than 1,200 patients who are beginning warfarin treatment. The knowledge gained in COAG will make significant scientific contributions to several medical specialties as well as the field of pharmacogenetics and personalized medicine.

→ For more information, see http://www.clinicaltrials.gov/ct2/show/NCT00839657
→ For more information, see http://coagstudy.org
→ (E) (**NHLBI**) (GPRA)

Multiple Sclerosis Research: Although the exact cause of multiple sclerosis (MS) is unknown, recent research supported by NIH has begun to identify genetic variations associated with increased risk for developing the disease. In 2007, a genome-wide association study with NIH support reported the first new genetic risk factors for MS to be identified in more than 20 years, and in 2009, meta-analyses and replication studies revealed additional new susceptibility genes. NIH also funds and conducts basic, translational, and clinical research on disease mechanisms, biomarkers, and treatments for MS. For example, NIH supports a randomized, double-blind, placebo-controlled Phase III trial (CombiRx) comparing the efficacy of treatment combining beta-interferon and glatiramer acetate vs. treatment with either agent alone for relapsing-remitting MS. The trial will determine whether combination therapy offers an improvement over the partial efficacy of either single treatment; it is the only direct comparison of these commonly used medications that is fully blinded and not supported by a commercial entity. NIH's Intramural Neuroimmunology Branch is collaborating with this trial to identify biomarkers associated with different clinical and treatment response profiles (BioMS). Such biomarkers may inform predictions about which treatment will most likely benefit a given patient, making this ancillary study an exciting addition to comparative effectiveness research in MS. Intramural investigators also will collaborate with the Swiss pharmaceutical company Santhera in a Phase I/II clinical trial to test the safety and efficacy of idebenone, which may protect against tissue damage, as a potential treatment for primary progressive MS.

→ De Jager PL, et al. *Nat Genet* 2009;41(7):776-82. PMID: 19525953. PMCID: PMC2757648.
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00211887
→ For more information, see http://clinicaltrials.gov/ct2/show/NCT00325988
→ For more information, see http://clinicaltrials.gov/ct2/show/study/NCT00950248
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Autoimmune Diseases*
→ (E, I) (**NINDS**)

Studies of Diabetes in Youth: NIH and CDC support the SEARCH for Diabetes in Youth study, which is providing key data on childhood diabetes incidence and prevalence. Recent data from SEARCH revealed unexpectedly high rates of diabetes in youth across most ethnic and racial groups in the United States. SEARCH also estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. To address the emerging problem of type 2 diabetes in youth, NIH supports the HEALTHY multicenter study to prevent risk factors for type 2 diabetes in middle-school children. A pilot study for HEALTHY found that an alarmingly high 15 percent of students in middle schools enrolling mainly minority youth had 3 major risk factors for type 2 diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease risk for obesity and diabetes. Thus, NIH launched the HEALTHY study in 2006. Half of the 42 participating middle schools receive the intervention, which includes changes to

school food service and physical education classes, behavior change, and communications campaigns. More than 70 percent of the enrolled students are from minority populations. For children who already have been diagnosed with type 2 diabetes, NIH supports the Treatment Options for Type 2 Diabetes in Youth (TODAY) study, which is comparing three different treatment strategies for children with the disease.

→ Mayer-Davis EJ, et al. *Diabetes Care* 2009;32 Suppl 2:S99-101. PMID: 19246580. PMCID: PMC2647691.
→ For more information, see http://www.searchfordiabetes.org/
→ For more information, see http://www.todaystudy.org/index.cgi
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIDDK**, CDC)

Preclinical and Clinical Research on Type 1 Diabetes: NIH's Type 1 Diabetes TrialNet is an international network that tests strategies for prevention and early treatment of type 1 diabetes. TrialNet recently found that the drug rituximab delayed progression of type 1 diabetes in newly diagnosed patients. To identify environmental triggers of type 1 diabetes, NIH established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium. TEDDY is enrolling newborns at high genetic risk and following them until age 15 to identify environmental triggers. NIH's landmark Diabetes Control and Complications Trial (DCCT) demonstrated that intensive control of blood glucose levels reduced complications of the eyes, nerves, and kidneys in type 1 diabetes patients. Long-term findings from the follow-on Epidemiology of Diabetes Interventions and Complications (EDIC) study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients begin intensive therapy as early as possible. To help patients achieve good glucose control, new initiatives focus on clinical and behavioral research related to new technologies for glucose control and insulin delivery (e.g., artificial pancreas technologies). NIH also supports research on islet transplantation through the Clinical Islet Transplantation Consortium. To provide resources for preclinical development of agents to test in clinical trials, NIH established the Type 1 Diabetes—Rapid Access to Intervention Development program.

→ Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group, et al. *Arch Intern Med* 2009;169(14):1307-16. PMID: 19636033. PMCID: PMC2866072.
Pescovitz MD, et al. *N Engl J Med* 2009;361(22):2143-52. PMID: 19940299.
→ For more information, see http://www.diabetestrialnet.org
→ For more information, see http://www.teddystudy.org
→ For more information, see http://diabetes.niddk.nih.gov/dm/pubs/control/
→ For more information, see http://www.citisletstudy.org/
→ For more information, see http://www.t1diabetes.nih.gov/T1D-RAID/
→ This example also appears in Chapter 2: *Autoimmune Diseases*
→ (E) (**NIDDK**, NCCAM, NCI, NIAID, NICHD)

Obesity, Inflammation, and Fat Cell Biology: NIH supports diverse research on fat (adipose) tissue, including studies that examine the relationship between obesity and inflammation in white adipose tissue, as well as research on another type of fat tissue, brown fat. In obese patients, lipid laden white adipose tissue secretes a number of proinflammatory molecules such as TNF-alpha (as well as other types of signaling molecules associated with insulin resistance). Chronic low-grade tissue inflammation observed in obese individuals has been linked to type 2 diabetes and cardiovascular disease risk. An NIH-funded, multicenter research study called Targeting INflammation using SALsalate for Type-2 Diabetes (TINSAL-T2D) has been initiated to determine whether salsalate, an inexpensive anti-inflammatory drug, could be a new treatment option for patients with type 2 diabetes. A different avenue of research led to the surprising discovery of metabolically active brown adipose tissue in adult humans. While white fat cells store fat, brown fat cells burn fat to

generate heat, and were once thought to exist only in infants. Research on brown fat in adult humans, as well as studies in animal models, may lead to novel strategies for obesity therapy.

→ Cypess AM, et al. *N Engl J Med* 2009;360(15):1509-17. PMID: 19357406. PMCID: PMC1986615.
Tseng YH, et al. *Nature* 2008;454(7207):1000-4.PMID: 18719589. PMCID: PMC2745972.
Seale P, et al. *Nature* 2008;454(7207):961-7. PMID: 18719582. PMCID: PMC2583329.
→ For more information, see http://tinsalt2d.org/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDDK**)

Look AHEAD (Action for Health in Diabetes): This NIH-led, multicenter, randomized clinical trial is examining the long-term health effects of an intensive lifestyle intervention (ILI) designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity. The study enrolled more than 5,100 overweight or obese adults with type 2 diabetes. Results from the first year of the study showed that participants in the ILI group achieved clinically significant weight loss; this was the case across all subgroups of the ethnically and demographically diverse study population. In addition, this weight loss was associated with an increase in "health-related quality of life" and improved cardiovascular fitness, blood pressure, cholesterol, and blood glucose, as compared to a control group receiving diabetes support and education. As another major point for health outcome measurement, the study recently completed 4 years of intervention and follow-up. In the coming years, continued follow-up of the Look AHEAD participants will show whether the ILI can reduce the incidence of heart attack and stroke and improve other health-related outcomes in this population. These findings will have important implications for treating type 2 diabetes.

→ For more information, see http://www2.niddk.nih.gov/Research/ClinicalResearch/ClinicalTrials/Patients/ClinicalResearchLookahead.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
→ (E/I) (**NIDDK**, CDC, NCMHD, NHLBI, NINR, ORWH) (GPRA)

Behavioral Strategies to Improve Quality of Life and Chronic Disease Outcomes: While health care advances continue to transform previously acute/fatal conditions into chronic conditions and individual life expectancy is increasing, issues of quality of life have become ever more important. Studies focusing on the management of disease- and treatment-related symptoms have demonstrated the capacity for behavioral strategies to mitigate effects of symptoms and contribute to improving short- and long-term patient outcomes. For example, behavioral strategies have been shown to improve patient outcomes across various diseases including diabetes, irritable bowel syndrome, and asthma. In recognition of the need for new behavioral strategies to manage chronic illness, NIH has established a goal of developing and testing behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes by 2012. Beginning in FY 2008, progress toward achieving this goal has been updated annually in the Online Performance Index section of NIH's portion of the President's budget submission to Congress.

→ For more information, see http://officeofbudget.od.nih.gov/br.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NINR**, NCI) (GPRA)

Developing Interventions to Improve Palliative Care at the End of Life: The life expectancy of the American people has reached a historic high, but along with increased life expectancy comes an increase in the number of people living with, and dying from, chronic debilitating diseases. Prolonged courses of decline at the end of life, palliative treatment options, and life-sustaining technologies have raised many important research questions within the last decade. In addition, the needs of dying children and their families are coming into greater focus, because death in childhood stands out as a

particular tragedy and a unique end-of-life experience for all involved. To address these needs, NIH-supported end-of-life science seeks to understand dying with respect to the needs of dying persons and formal and informal caregivers. It includes research on issues such as: alleviation of symptoms, psychological care, near-death preferences, advance directives, and family decision-making. Likewise, end-of-life research addresses the cultural, spiritual, age-specific, and disease-specific factors that make each person's experience at the end of life unique. In FY 2009, NIH announced a funding initiative to develop and test interventions to enhance end-of-life and palliative care that providers can implement across multiple settings, illnesses, and cultural contexts. NIH made the first awards under this solicitation in late FY 2009.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-09-004.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NINR**, NCI)

Intervention Reduces Risky Sexual Behavior Among Homeless HIV-Infected Adults: HIV infection in the United States is found more commonly among populations with significant life stressors, such as homelessness and drug use. An NIH-funded program (the Healthy Living Program) already shown to reduce risky sexual and substance abuse behavior among HIV-infected adults also appears to be effective in improving the lives of HIV-infected homeless or near-homeless adults. The program consisted of three intervention modules of five sessions each, designed to help participants reduce risky sexual behaviors and drug use, improve their quality of life, and sustain healthy behaviors. Compared with a control group who did not receive the Healthy Living Program intervention, individuals who were homeless or near-homeless in the 3 years prior to and during the study and who participated in the intervention engaged in 34 percent fewer risky sexual acts and 72 percent fewer sexual encounters with partners who were not infected with HIV or were of unknown HIV status. The study's results highlight the importance of programs designed to prevent or reduce the spread of HIV among people in high-risk populations. They also indicate that intervention programs focusing on skills development and including the physical and mental health needs of participants, are more likely to succeed than programs focusing only on reducing HIV transmission.

→ Rotheram-Borus MJ, et al. *Am J Public Health* 2009;99(6):1100-7. PMID: 18799777. PMCID: 2679793.
→ For more information, see http://www.nimh.nih.gov/science-news/2008/intervention-helps-reduce-risky-sexual-behavior-among-homeless-hiv-positive-adults.shtml
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIMH**)

Research Initiatives to Study Suicidality and Mental Health Needs of U.S. Army Soldiers and Returning Combat Veterans: The high rates of mental health and behavioral adjustment problems among recent U.S. military combat veterans, and the increasing rates of suicide among Army soldiers, are of growing concern. To address these issues, NIH is collaborating with the U.S. Army to evaluate selected groups of soldiers across all phases of Army service, including entry-level training and service, pre-deployment training, deployment and noncombat assignments, post-deployment, and post-separation reintegration to civilian life. The study's intent is to identify modifiable risk and protective factors, as well as moderators, of suicide-related behaviors. NIH also is launching a study of the impact of existing national, state, and local community-based programs addressing the adjustment and mental health needs of recent combat veterans, including returning National Guard, Army Reserve, and newly separated active duty personnel. This initiative will produce new information concerning effective strategies for fostering successful transition from combat to civilian roles for returning service members.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-140.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-070.html

→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIMH**)

Unexpectedly, Corneas from Older Donors Found Suitable for Transplantation: Light first enters the eye through the crystal clear cornea and is focused on the retina. Each year approximately 33,000 Americans undergo corneal transplants to replace diseased corneas that either become cloudy or no longer properly focus light, causing severe visual impairment. Corneal transplants are among the most common and successful transplantation procedures in medicine. Availability of donor tissue is key to this sight-restoring procedure. However, many eye banks refrain from harvesting tissue from donors over age 65 because of uncertainty about the integrity of older corneas. Newly instituted FDA regulations to further safeguard transplant recipients and the common use of LASIK surgery to correct refractive errors—which renders corneal tissue unusable for transplantation—could significantly limit future tissue supplies. The Cornea Donor Study (CDS) found that corneal transplants using tissue from donors ages 66-75 have similar success rates to those using tissue from donors ages 12-65. Based on these findings, the study authors recommend that the age limit for donor tissue could be safely expanded to age 75. The CDS study gives eye banks, transplant surgeons, and patients confidence in the use of older donor tissue, and should help eye banks keep pace with the demand for corneal tissue.

→ Cornea Donor Study Investigator Group, et al. *Ophthalmology* 2008;115(4):620-626.e6. PMID: 18387407.
→ For more information, see http://www.ophsource.org/periodicals/ophtha/article/PIIS0161642008000055/fulltext
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NEI**)

Evidence-Based Review Program: In FY 2001, NIH received a congressional mandate to review the current scientific evidence on the efficacy and safety of dietary supplements and identify research needs. NIH responded by developing an evidence-based review program using the Evidence-Based Practice Centers Program established by the Agency for Healthcare Research and Quality to conduct systematic reviews of the scientific literature and prepare reports of their findings. These reports have resulted in the publication of a number of articles in the peer-reviewed literature, and have helped NIH make decisions on research priorities in these areas. NIH ICs have found these reports invaluable in presenting what is and is not known in a research area, thus laying a sound foundation for identifying gaps in knowledge and providing a strong scientific basis for the development of a research agenda and for informing health policy decisions. Currently, NIH is sponsoring an evidence report on *Vitamin D and Calcium: Systematic Review of Health Outcomes* that will be considered by the IOM committee established to assess current relevant data and update as appropriate the Dietary Reference Intakes for vitamin D and calcium.

→ For more information, see http://ods.od.nih.gov/Research/EvidenceReports.aspx
→ (E) (**ODP/ODS**)

ClinicalTrials.gov: ClinicalTrials.gov was significantly modified during FY 2008-2009 to respond to new clinical trial registration and results reporting requirements established by the FDA Amendments Act of 2007 (PL 110-85). The existing registry was expanded to accommodate the submission of more information about a larger number of trials, including those trials of FDA-regulated drugs, biological products and devices that now are required to register. In addition, NIH developed and implemented results modules to accept and display to the public summary results information, including adverse event information from registered trials. Mandatory reporting of results began in September 2008, with mandatory submission of adverse event information following in September 2009. During FYs 2008-2009, more than 34,000 trials were newly registered with ClinicalTrials.gov, raising the total number of registered trials to 80,000. In addition, summary results of more than 830 clinical trials were submitted and made available at ClinicalTrials.gov, with the rate of results submission approaching 200 trials per month by the end of FY 2009. To solicit input on issues to be considered in rulemaking for further expansion of ClinicalTrials.gov, a public meeting was held in

April 2009; more than 200 participants attended the meeting, and more than 70 written comments were submitted to a public docket.

→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**NLM**)

Multicenter AIDS Study (MACS) Small Grant Opportunity: MACS is an ongoing (since 1984) epidemiological study in several U.S. cities of multi-ethnic/racial HIV-infected and HIV-uninfected men who have sex with men (MSM). A small grant funding opportunity is enhancing the value and potential for new knowledge from the MACS by examining drug use and HIV/AIDS among MSM over the life course. Studies will include an examination of social and behavioral risk factors and trajectories, the role of drug use in neurocognitive function, and other medical consequences. Findings from these studies may lead to new insights and interventions targeting this high-risk group. Such findings reinforce the importance of implementing interventions targeting drug reduction as part of comprehensive and efficacious HIV prevention program.

→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIAID**, NIDA, NIMH)

A Variety of Approaches Help Children Overcome Auditory Processing and Language Problems: Almost 7 percent of school-age children have difficulties learning and using language. Childhood language impairments can have lifelong effects on an individual's social life, academic career, and job aspirations. Each year, more than 1 million public school children receive interventions to address their language impairments. One very popular intervention is a commercially available software program called Fast ForWord Language (FFW-L; Scientific Learning Corporation, 1998). NIH-supported scientists conducted a randomized controlled trial of more than 200 children with language impairments, to assess whether those who used FFW-L had greater improvement in language skills than those who used one of two other methods, plus an active control group. The children in all three intervention groups demonstrated statistically significant improvement in both auditory processing and language skills. Thus, FFW-L did not provide a significant advantage over other types of interventions delivered in a similar intensive manner. Surprisingly, children in the active control group, which received individualized attention, instruction, and computerized testing on academic subjects but did not receive language intervention, also demonstrated significant improvement in auditory processing and language skills. This study demonstrated that all four methods improved the children's auditory processing and language skills. The data suggest that intensive programs focusing individualized attention on children with language impairments can improve language skills and preempt lifelong communication difficulties.

→ Tager-Flusberg H, Cooper J. *J Speech Lang Hear Res* 1999;42:1275-8. PMID: 10515521.
Gillam RB, et al. *J Speech Lang Hear Res* 2008;51(1):97-119. PMID: 18230858. PMCID: PMC2361096.
→ For more information, see http://www.nidcd.nih.gov/news/releases/08/01_30_08.htm
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIDCD**, NICHD)

Liver Disease Research: NIH supports clinical research to address the spectrum of liver diseases. The Nonalcoholic Steatohepatitis Clinical Research Network conducts placebo-controlled clinical trials of treatments for this condition, both in adults given pioglitazone or vitamin E, and in children given metformin or vitamin E. The Hepatitis B Clinical Research Network will conduct clinical trials to evaluate the effectiveness of different treatments and learn more about the natural history of this disease. The Childhood Liver Disease Research and Education Network combines and expands previous consortia focused on biliary atresia and cholestatic liver disease. This new network will foster discovery of new diagnostic

and treatment options for children with these diseases or who undergo liver transplantation, and support research training in rare pediatric liver diseases. Plans for another clinical network are beginning with a study to test whether immunosuppression minimization would be safe and thus beneficial in children several years after liver transplantation. The adult and pediatric Acute Liver Failure Study Groups address the problem of acute liver failure due to drugs or other factors. Current studies are testing potential therapies to improve survival. For example, results of a clinical trial to test intravenous N-acetylcysteine as a treatment for nonacetaminophen-related acute liver failure showed significant improvement in transplant-free survival in individuals who received therapy early in the course of their acute liver failure. The Drug-Induced Liver Injury Network conducts research aimed at understanding, diagnosing, and ultimately preventing liver toxicity due to drugs or complementary and alternative medicines. Future efforts of this network will focus on identifying genetic risk factors for drug-induced liver toxicity.

→ Lee WM, et al. *Gastroenterology* 2009;137(3):856-64, 864.e1. PMID: 19524577.
→ For more information, see http://www.jhucct.com/nash/
→ For more information, see http://dilin.dcri.duke.edu/
→ For more information, see http://www.utsouthwestern.edu/utsw/cda/dept25203/files/89624.html
→ For more information, see http://www.palfstudy.org/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDDK**, FDA, NCI, NICHD) (GPRA)

OHARA: The Oral HIV/AIDS Research Alliance: At the vanguard of basic, translational, and clinical research to combat the oral manifestations of HIV/AIDS is the NIH-funded Oral HIV/AIDS Research Alliance (OHARA), which drives and supports novel clinical studies in the United States and internationally to improve diagnosis, treatment, and management of comorbidities of AIDS-related oral complications, including necrotizing ulcers and tumors, fulminating fungal infections, and painful viral lesions that occur in almost all 33 million people infected worldwide. Their devastating effects compromise nutrition and exacerbate immune suppression in addition to the local effects. Even since the advent of antiretroviral therapy (ART), oral complications of AIDS remain a major public health problem. Though ART alleviates some symptoms, many oral lesions need additional specific treatment and globally, only 30 percent of HIV-infected individuals for whom ART is indicated receive it. The estimated prevalence of U.S cases of HIV/AIDS in 2006 exceeded 1.1 million, while about 56,300 people were newly infected with HIV that year. In its fourth year OHARA is making significant strides for people living with HIV/AIDS. OHARA is formed by world-expert scientists and clinicians. Its success is driven by three geographically and academically separate core units that provide expertise in epidemiology, mycology, and virology, embraced by a centralized NIH management and leadership. Currently, OHARA has ramped up eight clinical studies in various phases. They include studies to assess the clinical effectiveness of diagnostic tools for HIV/AIDS-related conditions, and compare the safety and efficacy of novel treatments and preventive strategies for HIV/AIDS-related oral diseases and malignancies.

→ Shiboski CH, et al. *J Oral Pathol Med* 2009;38(6):481-8. PMID: 19594839.
Jacobson MA, et al. *PLoS One* 2009;4(4):e5277. PMID: 19381272. PMCID: PMC2667217.
→ For more information, see http://aactg.org/committees/scientific/optimization-co-infection-and-co-morbidity-management/subcommittees/ohara-sub-3
→ For more information, see http://www.nidcr.nih.gov/Research/DER/IntegrativeBiologyAndInfectiousDiseases/AIDSImmuno.htm
→ For more information, see http://aactg.org/about-actg
→ For more information, see http://www.who.int/hiv/data/en/
→ For more information, see http://www.cdc.gov/hiv/topics/surveillance/basic.htm#Main
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIDCR**, NIAID)

Research on Bariatric Surgery: The multicenter NIH-funded Longitudinal Assessment of Bariatric Surgery (LABS) consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Results from this study have been published in the *New England Journal of Medicine*. The study also addresses comparative effectiveness with respect to its collection of data on surgical procedures and pre- and post-operative information. Because bariatric surgery also is used in clinical practice sometimes as a treatment for severely obese adolescents, NIH additionally is supporting an observational study of teens already scheduled for surgery, Teen-LABS, to collect data to help determine whether it is an appropriate treatment option for extremely obese adolescents. A pilot study also is being conducted using the new Metabolic Clinical Research Unit at the NIH CC to examine changes in insulin resistance after bariatric surgery. To further explore the observation that certain bariatric surgical procedures are associated with amelioration of obesity-related insulin resistance and diabetes soon after surgery, and thus independent of weight loss, NIH issued a funding opportunity announcement to encourage research in this area.

→ Adams TD, et al. *N Engl J Med* 2007;357(8):753-61. PMID: 17715409.
The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. *N Engl J Med* 2009;316(5):445-54. PMID: 19641201.
→ For more information, see http://win.niddk.nih.gov/publications/labs.htm
→ For more information, see http://www.nih.gov/news/pr/apr2007/niddk-16.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E/I) (**NIDDK**, ORWH)

Urology Research: The Urinary Incontinence Treatment Network (UITN) conducts long-term studies and clinical trials of the most commonly used surgical, pharmacological, and behavioral approaches for management of urinary incontinence in women diagnosed with stress and mixed incontinence. Recently, a different group of investigators completed the Program to Reduce Incontinence by Diet and Exercise (PRIDE) study and determined that a weight loss program could reduce significantly the frequency of urinary incontinence in overweight and obese women. Several studies address interstitial cystitis/painful bladder syndrome (IC/PBS), a urologic condition whose prevalence is uncertain and which remains difficult to diagnose and treat. The RAND Interstitial Cystitis Epidemiology (RICE) study is designed to estimate the prevalence of interstitial cystitis and establish a working definition of this condition. The Boston Area Community Health (BACH) Survey is a population-based study of urologic conditions, including IC/PBS, in more than 5,500 adults. Results emerging from BACH about IC/PBS will provide a clearer picture on the IC/PBS burden in the population, and will inform research efforts to reverse this burden. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is designed to enhance understanding of the major urological chronic pelvic pain disorders, including IC/PBS and chronic prostatitis/chronic pelvic pain syndrome.

→ Burgio KL, et al. *Ann Int Med* 2008;149:161-9. PMID: 18678843.
Subak LL, et al. *N Eng J Med* 2009;360(5):481-90. PMID: 19179316.
→ For more information, see http://www.uitn.net/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIDDK**, NICHD)

Improving the Lives of Asthmatic Children in the Inner City: The NIH Inner-City Asthma Consortium (ICAC) of 10 academic clinical centers, launched in 2002, evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. The Consortium also pursues studies to understand mechanisms underlying the onset and progression of asthma and research to develop diagnostic and prognostic biomarkers. An ICAC longitudinal birth cohort study involving 500 inner-city children is investigating the immunologic causes of the development of recurrent wheezing, which can be indicative of asthma in children under age 3. ICAC has

extended the study to follow all participant children to age 7, when the diagnosis of asthma can be definitive. Researchers hope to identify immunologic characteristics that will predict the development and severity of asthma at a later age. ICAC researchers are conducting two clinical trials to determine the safety, dosing levels, and biologic activity of a potential new allergy immunotherapy for cockroach allergen, which ICAC studies previously found to be a major determinant of asthma severity among inner-city children. Finally, an ICAC clinical trial assessed the benefit of using exhaled nitric oxide (NO) as a marker for asthma management. Although the study reinforced the importance of the NIH asthma guidelines for disease control, it did not find that measuring exhaled NO provided any additional clinical benefit.

→ Szefler SJ, et al. *Lancet* 2008;372(9643):1065-72. PMID: 18805335. PMCID: PMC2610850.
→ For more information, see http://www3.niaid.nih.gov/topics/asthma/research/researchActivities.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIAID**)

Rural Latino Preschooler's Oral Health: Intersections among Family, Community, Providers and Regulators: Latino children experience among the highest prevalence of early childhood dental caries in the United States. Researchers explored the intersections among four societal sectors or contexts of care that potentially contribute to oral health disparities for low-income, preschool Latino children in rural California. The ethnographic investigation was conducted in a predominately Mexican-American agricultural community. Observations occurred in homes, community facilities, and dental offices, and were supplemented with in-depth interviews by trained anthropologists with key community informants and primary caregivers of children less than 6 years old. Factors that significantly intersected to produce or sustain poor oral health care for children follow. Caregivers did not always recognize signs of decay among their children, nor quickly respond unless children also complained of pain. Fluctuating eligibility for health insurance intersected with limited community infrastructure and civic amenities, including lack of public transportation, to create difficulties in access to care. Nonfluoridated bottled water often was consumed rather than tap water because of fears about potential pesticide pollution of the municipal water supply. Multiple dental visits caused parental hardship and occasionally resulted in the loss of the caregiver's job. Dental fear and poor provider-caregiver communication were exacerbated by a scarcity of dentists willing to serve rural low-income populations. Such empirical research related to newly emerging conceptual models is greatly needed. Understanding that multiple, intersecting factors at numerous levels will inform intervention research customized to the individual, community, and society.

→ Barker JC, Horton SB. *BMC Oral Health* 2008;8:8. PMID: 18377660. PMCID: PMC2362117.
→ For more information, see http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/DentalCaries/DentalCariesChildren2to11
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIDCR**)

Alzheimer's Disease Cooperative Study (ADCS): Much of the AD-related clinical research supported by NIH takes place through the ADCS. The study involves a consortium of centers in the U.S. and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of AD or predict development of the disease in vulnerable people. To date, approximately 4,600 people have participated in the trials. Five new trials are underway through ADCS. These include: (1) a trial to examine whether treatment with DHA, an omega-3 fatty acid, will slow decline in AD; (2) a multicenter trial to evaluate home-based assessment methods for AD prevention research in people age 75 or older; (3) a trial to evaluate the efficacy and safety of 18 months of treatment with the drug PF-04494700 (TTP488), an oral compound formulated to prevent amyloid beta from binding to a specific brain receptor; (4) a trial of valproate, an anticonvulsant drug, to determine its ability to delay the emergence of agitation and psychosis and possibly the clinical progression of AD; and (5) a trial of intravenous immunoglobulin, which contains naturally occurring antibodies against beta-amyloid, to establish its clinical utility for treating AD. This program is a cornerstone of the NIH

GPRA goal to: "By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

- → For more information, see http://www.adcs.org/Default.aspx
- → This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- → (E) (**NIA**) (GPRA)

Interventions to Remediate Age-Related Cognitive Decline: Age-related cognitive decline distinct from dementia will affect most older individuals to some extent and has a direct impact on their independence and vitality. Cognitive training, physical exercise, enhancement of self-efficacy, social engagement, diet, environmental enrichment, and stress reduction have all been shown to have positive effects on cognition; however, the quality of this evidence varies widely across studies. NIH, in partnership with the McKnight Brain Research Foundation in conjunction with the Foundation for NIH, has initiated a program to convert insights from previous work in cognitive aging into feasible intervention strategies that can be tested in randomized clinical trials. The program's primary goal is to support the initial development and pilot testing of behavioral interventions (individually and in combination) to establish their feasibility, the likely strength of their effects, and immediate and short-term efficacy. These early steps should allow these interventions to move to new clinical trials.

- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-09-009.html
- → This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- → (E) (**NIA**)

Comparative Effectiveness Study of Drugs for Age-Related Macular Degeneration: Lucentis was approved by FDA in 2006 for treatment of advanced age-related macular degeneration (AMD), a leading cause of vision loss in older Americans. Though the drug is safe and effective, it is expensive—approximately $2,000 per month—and repeated injections are required. Avastin is a similar pharmaceutical but is far less expensive—approximately $100 per month—and also has been used extensively in treating patients with AMD. Most retinal specialists think that Avastin is a safe and effective alternative to Lucentis. To resolve this question, NIH is funding the Comparison of AMD Treatments Trial (CATT), a multicenter, randomized, clinical trial to compare the safety and efficacy of Avastin and Lucentis, and to explore less-frequent treatment schedules for both drugs. The first participants were randomized in early 2008. If Avastin proves to be comparable to Lucentis, the cost savings could reach $2-3 billion per year. Less frequent treatment schedules also would lower costs, reduce treatment risk, and improve patient quality-of-life.

- → For more information, see http://www.nei.nih.gov/news/pressreleases/022208.asp
- → This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- → (E) (**NEI**)

Promising Clinical Trials of Gene Transfer for Severe Childhood Eye Disease: Leber congenital amaurosis (LCA) is an early-onset, severe retinal disease that results from mutations in any 1 of 13 genes. One form of LCA results from mutations in a gene called RPE65. In 1993, NIH intramural scientists discovered that RPE65 plays a key role in the visual cycle, the set of biochemical interactions that converts light into an electrical signal to initiate vision. Mutations in RPE65 were found to disrupt the visual cycle, resulting in LCA and blindness. Retinal cells in children with LCA remain viable for several years, providing a window of opportunity to intervene therapeutically. An NIH-supported Phase I clinical trial of RPE65 gene transfer in LCA found the treatment is safe and that visual function improved. Two other independent Phase I clinical trials of RPE65 gene transfer also found evidence of visual improvement, but further work is needed to

develop the therapeutic potential fully. Ongoing studies are exploring the range of therapeutic doses in adult and adolescent patients as well as rigorous evaluation of the effectiveness of this treatment. Gene transfer is particularly well-suited to the treatment of eye disease. This clinical trial is an important step in treating LCA and in establishing proof-of-concept for gene transfer as a viable therapy for eye disease.

→ Cideciyan AV, et al. *Proc Natl Acad Sci U S A* 2008;30;105(39):15112-7. PMID: 18809924. PMCID: PMC2567501.
→ For more information, see http://www.pnas.org/content/105/39/15112.long
→ For more information, see http://www.nei.nih.gov/lca/
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NEI**)

Clinical Research Networks: Clinical research is essential for translating laboratory findings into evidence-based interventions targeting an array of public health concerns. Many research programs involve collaborative networks, drawing scientists together to bring the benefits of clinical research to high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. Among such networks that have generated significant findings to advance medical practice and improve public health are the Maternal and Fetal Medicine Network, Neonatal Research Network, Obstetric Pharmacology Research Network, Pediatric Critical Care Research Network, Pelvic Floor Disorders Network, Traumatic Brain Injury Clinical Trials Network, and Global Network for Women's and Children's Health Research.

→ For more information, see http://www.bsc.gwu.edu/mfmu/index.html
→ For more information, see https://neonatal.rti.org
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-002.html
→ For more information, see http://www.cpccrn.org
→ For more information, see http://www.pfdnetwork.org
→ For more information, see http://www.tbi-ct.org/
→ For more information, see http://gn.rti.org/about/index.cfm
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NICHD**, FIC, NCCAM, NCI, NIDCR, ORWH)

Clinical Trials Network: NCI-supported clinical trials networks share resources and pool data to promote and support the study of new cancer treatments, methods of cancer prevention and early detection, and quality-of-life and rehabilitation issues. The 65 NCI-designated Cancer Centers serve as a major platform for these trials. NCI is restructuring the Clinical Trials Enterprise. Initiatives include: Standard Terms of Agreement for Research Trials, the Clinical Trials Reporting Program, correlative studies (e.g., biomarkers, imaging, and quality-of-life studies) embedded in clinical trials, disease-specific and patient advocate steering committees, and acceleration of translational research. The Community Clinical Oncology Program recently stopped the Selenium and Vitamin E Cancer Prevention Trial. Initial data analysis showed that selenium and vitamin E supplements, taken either alone or together for an average of 5 years, did not prevent prostate cancer. Recent findings from NCI's Cooperative Group Program include a gene abnormality that predicts childhood leukemia relapse, the role of the ch14.18 monoclonal antibody in the treatment of high-risk neuroblastoma, and the usefulness of CT colonography in detection of large adenomas and cancers. Year 2 accomplishments of the NCI Community Cancer Centers Program include increased patient and physician involvement in NCI-sponsored trials, new methods for tracking minority accrual, and improved specimen collection. The Pediatric Oncology Branch of the NCI Center for Cancer Research (CCR) is coordinating a neurofibromatosis clinical trials program to develop effective therapies for this disease. The CCR also is conducting trials for patients with androgen-independent and metastatic prostate cancer using anti-angiogenic compounds as well as novel immunotherapies and immunologic strategies.

→ For more information, see http://restructuringtrials.cancer.gov/
→ For more information, see http://prevention.cancer.gov/programs-resources/groups/copt/programs/about
→ For more information, see http://www.cancer.gov/clinicaltrials/digestpage/SELECT/
→ For more information, see http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group
→ For more information, see http://target.cancer.gov/newsroom/news/01_07_09.aspx
→ For more information, see http://ncccp.cancer.gov
→ For more information, see http://content.nejm.org/cgi/content/full/359/12/1207
→ For more information, see http://ccr.cancer.gov
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NCI**) (GPRA)

NIH Undiagnosed Diseases Program (UDP): In May 2008, NIH launched a program to evaluate patients with disorders that have evaded a diagnosis. Often patients seek help from multiple physicians and other health care providers over many years without receiving a diagnosis. Using a unique combination of 35 NIH scientific and medical specialty experts, the UDP pursues three goals: To help patients with unknown disorders reach an accurate diagnosis, to discover new diseases that provide insight into human biology, and to reestablish the NIH CC as the referral Center for mystery diseases. In its first year, the UDP received more than 2,000 inquiries, with approximately half of them of neurological origin, and 100 of them pediatric. Of the 2,000 inquiries in the first year, 850 were followed up with submission of medical records; 450 of the applications to participate in the program were deemed inappropriate; and 158 cases were accepted into the program by 10 Institutes and Centers. The program is trans-NIH in scope. Senior attending physicians with many different medical specialties from NIH research Centers and Institutes contribute the expertise needed to achieve the goals of this clinical research program. Any longstanding medical condition that eludes diagnosis by a referring physician can be considered undiagnosed and may be of clinical interest.

→ For more information, see http://rarediseases.info.nih.gov/Resources.aspx?PageID=31
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**ODP/ORDR, CC, NHGRI**, NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIMH, NINDS, NINR)

Specialized Centers of Research (SCORs) on Sex and Gender Factors: The SCORs on Sex and Gender Factors Affecting Women's Health provide an innovative and interdisciplinary approach to advancing research on the influence of sex and gender as it relates to health and disease. Each of these SCORs emphasizes research in an area of clinical importance to women's health. The 11 current SCORs, co-funded with five NIH ICs and the Food and Drug Administration, address sex/gender research in the areas of depression, pain, urinary tract infection, reproductive issues, substance abuse, and osteoporosis. An example of scientific advances includes the isolation of an estrogen receptor alpha signaling process that therapeutically could be downregulated to reduce the risk for obesity and type 2 diabetes in menopausal women. In 2009, the SCORs contributed 116 journal articles, 176 abstracts, and 63 other publications (reviews and book chapters) resulting from their research.

→ For more information, see http://orwh.od.nih.gov/interdisciplinary/SCORs.html
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**ORWH**, FDA, NIAMS, NICHD, NIDA, NIDDK, NIMH)

Compliance with the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research: NIH works to ensure compliance with the NIH Policy for the Inclusion of Women and Minorities as Subjects in Clinical Research by convening a trans-NIH committee that addresses consistency in inclusion policy implementation and investigator reporting of population data. Over the past 2 years, NIH has focused on analyzing and streamlining the data reporting process, reemphasizing the vital role of NIH staff to monitor adherence of the NIH Inclusion policy and management of grants, contracts, and cooperative agreements that involve human subjects research. The role of peer

reviewers and investigators in meeting policy requirements continues to be stressed. NIH compiled the annual aggregate comprehensive reports: *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research* and the *2009 Biennial Report Certifying IC Compliance with the Inclusion Guidelines* based upon IC Advisory Council reviews, as required by statute.

→ For more information, see http://orwh.od.nih.gov/inclusion.html
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E/I) (**ORWH**, OER, OIR)

Developing Biodefense Vaccines and Therapeutics: NIH is the lead Federal agency within HHS for conducting and supporting research on potential agents of bioterrorism and emerging infectious diseases that directly affect human health. NIAID is the lead Institute within NIH in this area. Counter measures against NIAID Category A-C priority pathogens, microbes, and toxins, which are considered to be the most significant threats to the Nation's well-being, are either nonexistent, of limited utility, or threatened by the emergence of antimicrobial resistance or intentional engineering to increase virulence or decrease drug susceptibility. Given the absence of a substantial commercial market, regulatory hurdles, and extensive clinical trial requirements, the private sector has little incentive to invest in countermeasures. To remedy this situation, NIH supports unique partnerships among government, industry, small businesses, and academia to facilitate the movement of promising products through all stages of the drug research and development pipeline, with the goal of developing vaccines and therapeutics against diseases such as smallpox and botulism, as well as for infections with Ebola, Marburg, and West Nile virus infection. NIH advances include progress toward vaccines and/or therapeutics for anthrax, smallpox, and West Nile viruses. NIH supported development of a nonhuman primate model for plague; studies in the model have been completed for three licensed antibiotics for plague. In addition, advanced development and production continues for a recombinant protective antigen vaccine for anthrax and a modified vaccinia Ankara vaccine for smallpox.

→ For more information, see http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E/I) (**NIAID**)

NIEHS Clinical Research Unit: NIEHS focuses its research mission on environmental effects on human health, an area where human research data often are lacking. To improve the translation of basic research to human health, the NIEHS is expanding its Clinical Research Program (CRP). NIEHS has opened a new Clinical Research Unit (CRU) on the Research Triangle Park, NC, campus. The mission of the CRP is to translate basic laboratory findings to humans; study interactions between genetic susceptibility and environmental factors in the pathogenesis of complex human traits and diseases; and identify populations at risk and develop novel preventative and therapeutic strategies to combat human diseases. The CRU will provide support for the development of clinical research protocols; provide patient screening, recruitment and enrollment functions for NIEHS clinical studies; provide basic sample processing support (e.g., clinical labs and cell isolation); and provide support for specialized clinical procedures and services with the ultimate vision of fostering substantial onsite clinical research activity. Examples of the kinds of studies that will be supported by the CRU include the following: collection of tissue and body fluid samples for *ex vivo* human studies; investigation of host response to environmental exposures; Phase I-II-III clinical trials; environmental intervention studies; and phenotyping of selected individuals from NIEHS research populations such as the Environmental Polymorphism Registry. The CRU will be an integral part of the NIEHS intramural research portfolio and will provide support to a substantial number of NIEHS scientists.

→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (I) (**NIEHS**)

Putting Clinical Research Results into Practice

Genotyping Information for Use in Warfarin Therapy: The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB), a component of the Pharmacogenetics Research Network (PGRN), sponsors data-sharing consortia. In 2009, one of the consortia, the International Warfarin Pharmacogenetics Consortium (IWPC), completed its first project: Clinical and genetic data from more than 4,000 patients worldwide who received warfarin were assembled into a large dataset to create a universal dose algorithm that incorporated genetic factors along with clinical factors. This established a better method to calculate the initial dose of the anticoagulant, and NIH will use the information for a prospective clinical trial to determine the value of pre-prescription genotyping. Further genomic analyses of the warfarin data set are underway. Based upon the success in this endeavor, more consortia were created in 2009. The International Tamoxifen Pharmacogenetics Consortium (ITPC) was formed to gather genetic and clinical data on the efficacy and toxicity of tamoxifen from patients around the world to test for specific associations between genetic variants and clinical effects, and the International Severe Irinotecan Neutropenia Consortium (INSINC) was formed to assemble a large dataset to answer questions definitively relating to genetic effects on adverse outcomes of irinotecan therapy, and to provide tools for evaluating toxicity risk.

- → International Warfarin Pharmacogenetics Consortium, et al. *N Engl J Med* 2009;360(8):753-64. PMID: 19228618. PMCID: PMC2722908.
- → For more information, see http://www.nigms.nih.gov/Initiatives/PGRN
- → For more information, see http://www.pharmgkb.org/views/loadConsortia.action
- → This example also appears in Chapter 3: *Genomics*
- → (E) (**NIGMS**, NCRR, NHLBI, NINDS) (GPRA)

Workshop on Assessing Cost-Effectiveness in Clinical Research: Cost-effectiveness analysis (CEA) has been an ongoing element of the NIH clinical research portfolio for many decades. It is a close relative of comparative effectiveness research and, as a tool, can be applied usefully to data from either efficacy or effectiveness studies. CEA accounts for a small but important proportion of overall NIH research expenditures, totaling $49 million in FY 2008. It comprises a relevant issue for scientists, health care providers, patients, families, and caregivers. In continuing its research tradition, in July of 2008, NIH hosted a workshop titled, "Integrating Cost-Effective Analysis into Clinical Research" in order to build a foundation for identifying interventions that will improve both health outcomes and the cost effectiveness of treatments. Building on workshop results, NIH issued the RFA "Incorporating Cost-Effectiveness Analysis into Factors Affecting Quality-of-Life Health Related Research (R01)" (RFA-NR-09-005). This Funding Opportunity Announcement solicits applications to study the cost effectiveness of interventions that will improve health outcomes.

- → For more information, see http://www.ninr.nih.gov/NewsAndInformation/MeetingSummariesandReports
- → For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-09-005.html
- → (E, O) (**NINR**, NCI, ODP/ODS, ODP/ORDR)

NIH Consensus Development Program: This program, administered by the Office of Medical Applications of Research (OMAR) within the Office of the Director, NIH, was established in 1977 as a mechanism to assess, translate, and disseminate the results of biomedical research. Since its inception, OMAR has conducted more than 120 Consensus Development Conferences, and 30 State-of-the-Science (formerly "Technology Assessment") Conferences. The program generates evidence-based statements addressing controversial issues in medicine and public health that are useful and relevant for health care providers, policymakers, patients, researchers, and the general public. The conferences are structured around key questions, including questions on the efficacy, risks, and clinical applications of a technology, along with current gaps in knowledge to help formulate directions for future research. For every conference, a systematic evidence review is performed through a partnership with the Agency for Healthcare Research and Quality to serve as the foundation upon which the conference will build. Experts in the field provide additional input and insights through several

days of oral presentations. The conferences also contain sessions for public input and discussion. A multidisciplinary, nonadvocacy, independent panel free from scientific or financial conflicts considers all of this information, and then writes a statement answering the posed conference questions. Consensus and state-of-the-science statements are disseminated widely after the conference to either impact clinical practice—when evidence strongly supports the use (or avoidance) of a particular intervention—or to direct future research—when important gaps in knowledge have been identified. Upcoming conferences in 2010 include: Enhancing Use and Quality of Colorectal Cancer Screening; Lactose Intolerance and Health; Vaginal Birth After Cesarean: New Insights; Preventing Alzheimer's Disease and Cognitive Decline; and Inhaled Nitric Oxide Therapy for Preterm Infants.

→ For more information, see http://consensus.nih.gov/
→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (E) (**ODP/OMAR**)

Family Satisfaction During Decisions to Withdraw Life Support: Clinicians in the intensive care unit (ICU) often care for patients who are on several life support measures simultaneously. When such a patient is dying and the decision is reached to withdraw life support, these clinicians may make an imperfect compromise in seeking to balance the complex needs of the patient and the patient's family—they may remove the life support measures one at a time over a period of days, rather than withdrawing all at once. This practice, referred to as sequential withdrawal, may be relatively common, and may have a varying impact on the family's satisfaction with ICU care. The research team examined the life support withdrawal process for 584 patients who died in the ICU or within 24 hours of discharge from the ICU, and surveyed the family members regarding their perceptions of the care provided. When surveyed 1 to 2 months after the death of the patient, family members of patients who had a short ICU stay reported a lower satisfaction with the ICU care if the withdrawal process was extended over more than 1 day. However, for family members of patients who had a long ICU stay (8 days or more), satisfaction with care increased with a more extended duration of the withdrawal. In addition, family satisfaction with care was higher if the patient was off the ventilator at the time of death. Withdrawal of life support is a complex process that depends on patient and family characteristics; however, sequential withdrawal of life support is a frequent phenomenon that sometimes seems to be associated with family satisfaction.

→ Gerstel E, et al. *Am J Respir Crit Care Med* 2008;178(8):798-804. PMID: 18703787. PMCID: PMC2566791.
→ For more information, see http://www.nih.gov/news/health/oct2008/ninr-15.htm
→ For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18703787
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NINR**)

Centers in Self-Management or End-of-Life Research: Future progress in improving the ability of those with chronic disease at all stages of life to manage their own illness, as well as improving the care of patients at the end of life, will require the development of enhanced research capacity, including more trained investigators and expanded institutional resources. In early 2007, NIH solicited applications for the Centers in Self-Management or End-of-Life Research. These Centers are expected to serve as a nexus for the emergence of self-management and end-of-life research as interdisciplinary sciences. They will train investigators from multiple backgrounds and leverage collaborations to increase the quantity and quality of innovative, interventional research projects. To date, six grants have been awarded from this solicitation. These Centers focus on a variety of topics, such as the self-management of chronic illnesses in Hawaii, biobehavioral research in self-management of cardiopulmonary disease, evidence-based practice in the underserved, and end-of-life transition research.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-004.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-005.html

→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NINR**)

Support for Research on the Dissemination, Implementation, and Operation of HIV Preventive Interventions: NIH continues to support research on all aspects of HIV preventive interventions. While effective preventive interventions have been developed, there is a recognized gap between their development and their later uptake by community-level service providers. In FY 2008, NIH issued a funding opportunity announcement (FOA) to encourage research ensuring that these interventions are adopted and effectively implemented. The FOA invites applications for research projects that will enhance technology transfer, dissemination, implementation, and operational research related to evidence-based HIV preventive interventions. Staff from NIH and the Centers for Disease Control and Prevention collaborated in the development of this FOA by identifying research gaps and opportunities in these areas. Five categories of projects, in particular, were identified in which additional research activities could assist in the effective and efficient implementation of HIV preventive interventions: dissemination strategies, adoption of interventions, implementation fidelity and adaptation, intervention effectiveness, and sustainability of interventions.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-166.html
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIMH**, CDC, NICHD, NINR)

Rapid HIV Testing Clinical Trial: HIV testing is an important component of HIV prevention. To help prevent late diagnosis and HIV spread, NIH is working to identify and address the cultural barriers to making HIV screening more acceptable and to strengthen the link between education, testing and counseling, and treatment within all ethnic groups. NIH-supported modeling research has shown that routine HIV screening, even among populations with prevalence rates as low as 1 percent, is as cost-effective as screening for other conditions such as breast cancer and high blood pressure. Still, little is known about whether offering testing in the absence of counseling influences patient acceptance or how they receive results. How and whether testing absent counseling influences HIV risk behaviors among those who are HIV negative also remains to be determined. Indeed, the Institute of Medicine has recommended comparison research to include significant prevention counseling as a key variable. In this regard, a randomized controlled clinical trial—taking place in NIH's Drug Abuse Treatment Clinical Trials Network—is recruiting individuals receiving drug abuse treatment to participate in a multicenter HIV testing and counseling study. The study will assess the relative effectiveness of on-site HIV rapid testing with brief, participant-tailored prevention counseling as compared with (1) on-site testing with information only and (2) referral for off-site HIV testing. HIV screening has important public health implications, recognized by the Centers for Disease Control and Prevention, which has called for increased HIV screening as part of its recommended guidelines. NIH is eager to advance new HIV rapid-screen technologies and counseling in community drug treatment programs and in criminal justice settings.

→ For more information, see http://www.drugabuse.gov/about/organization/arp
→ For more information, see http://www.drugabuse.gov/CTN/protocol/0032.html
→ For more information, see http://www.drugabuse.gov/about/organization/arp
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIDA**)

HIV Topical Microbicides: Topical microbicides are small molecule prophylactic treatments to prevent the transmission and spread of HIV. Guided by the NIAID Topical Microbicide Strategic Plan, NIH is funding a number of microbicide research studies through the Microbicide Trials Network (MTN), the HIV Prevention Trials Network (HPTN), and the Microbicide Innovation Program (MIP). The microbicides under investigation are designed to prevent HIV transmission by killing or inactivating microbial pathogens, strengthening the body's normal defenses, blocking attachment of HIV to

susceptible cells, and preventing HIV from spreading to other uninfected cells. Microbicides typically are administered via a gel, foam, or cream intended to prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically inside the vagina or rectum. In February 2009, NIH-supported researchers found that an investigational vaginal gel called PRO 2000, intended to prevent HIV infection in women, is safe and approximately 30 percent effective (33 percent effectiveness would have been considered statistically significant). While additional data are needed to determine if PRO 2000 protects women from HIV infection, it was the first human clinical study to suggest that a microbicide may prevent male-to-female sexual transmission of HIV infection.

→ For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/prevention/research/Microbicides/research.htm
→ For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/HPTN_035_gel.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIAID**, NICHD, NIMH)

Veterans With HIV and Alcohol Problems: The Veteran's Aging Cohort Study (VACS), a cooperative agreement between NIH and the Department of Veterans Affairs, focuses on HIV-infected veterans with alcohol use disorders. Alcohol abuse and dependence occur in approximately 25 percent of veterans. This work informs the design of interventions to modify the risk of alcohol- and liver-related mortality associated with HIV. The VACS index, which predicts health outcomes including HIV disease progression, was developed and is being evaluated as a clinically informative index for this study. Alcohol measures that can be used readily in HIV clinical settings have been validated and will guide the intensity of the alcohol intervention. Determining the presence of other health comorbidities and the level of antiretroviral adherence will help prioritize clinical care. Collaborations between VACS and other large studies will determine the generalizability of studies with veterans to other populations and inform use of electronic medical records from clinical samples with complex diseases for scientific research. This study also has evaluated the associations of "non-HIV" conditions (e.g. HCV, cardiovascular health) with alcohol, HIV, HIV treatment, and aging, and contributed data to all three international cross cohort collaborations—North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), ART Cohort Collaboration (ART-CC), and HIV Cohorts Analyzed Using Structural Approaches to Longitudinal data (HIV CAUSAL)—addressing the question of when to start antiretroviral therapy. Progress of the VACS Study includes: enrollment of 7,015 patients, launch of a fourth follow-up survey (February 2008), and completion of blood and DNA collection and the initiated dissemination of tissue samples to researchers across the country. VACS also participates in collaborative grants, including those from the Veterans Affairs Health Services Research and Development Service, NIH, and the Medical Research Council UK.

→ For more information, see http://www.vacohort.org
→ For more information, see http://statepiaps.jhsph.edu/naaccord/
→ For more information, see http://www.epi.bris.ac.uk/art-cohort/index.htm
→ For more information, see http://www.hsph.harvard.edu/faculty/miguel-hernan/hiv-causal
→ (E) (**NIAAA**)

BARI 2D Clinical Trial: Cardiovascular disease (CVD) is the leading cause of diabetes-related deaths—about 65 percent of people with diabetes die of heart disease or stroke. Recognizing the importance of comparative effectiveness research, NIH in FY 2000 awarded support for the BARI 2D clinical trial to evaluate management strategies for patients with stable coronary artery disease and type 2 diabetes. Its goal was to determine whether mortality and CVD event rates could be reduced by early coronary revascularization and intensive medical therapy compared with intensive medical therapy alone, and by an initial strategy of insulin sensitization compared with provision of insulin to treat hyperglycemia. The trial found that neither early revascularization nor insulin sensitization was superior to the tested alternatives in terms of CVD event rates. However, among patients for whom bypass surgery was deemed to be the appropriate revascularization procedure, prompt revascularization reduced the rate of major, nonfatal CVD events such as heart attack and stroke.

→ BARI 2D Study Group, et al. *N Engl J Med* 2009;360(24):2503-15. PMID: 19502645.
→ For more information, see http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?
→ For more information, see http://content.nejm.org/cgi/reprint/360/24/2503.pdf
→ For more information, see http://content.nejm.org/cgi/reprint/360/24/2570.pdf
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NHLBI**, NIDDK)

Action to Control Cardiovascular Risk in Diabetes (ACCORD): ACCORD is a multicenter randomized clinical trial of 10,251 persons with type 2 diabetes who are at high risk of a cardiovascular disease (CVD) event. It was designed to assess whether the rate of major CVD events could be reduced by intensive control of blood sugar (glycemia) compared with the current standard of care, intensive control of blood pressure compared with the current standard of care, or treatment of blood lipids with fibrate plus statins compared with treatment with statins alone. On February 6, 2008, NIH announced that participants receiving intensive glycemia treatment would be transitioned to the ACCORD standard treatment approach because higher mortality was observed among them. The glycemia main results were published in the *New England Journal of Medicine* in June 2008. They have substantial implications for the clinical treatment of diabetes, especially in older patients at high risk of CVD. The blood pressure and lipid trials are continuing as designed, with the last patient visits completed in June 2009.

→ Action to Control Cardiovascular Risk in Diabetes Study Group, et al. *N Engl J Med* 2008;358(24):2545-59. PMID: 18539917.
→ For more information, see http://clinicaltrials.gov/ct2/show/
→ For more information, see http://www.accordtrial.org
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NHLBI**, CDC, NEI, NIA, NIDDK)

Diabetes Prevention Program Outcomes Study (DPPOS) and Translational Research: The landmark NIH Diabetes Prevention Program (DPP) clinical trial showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk. This finding was true across all participating ethnic groups and for both men and women. The DPPOS is a long-term follow-up study of the DPP participants that is determining the durability of the interventions in preventing or delaying type 2 diabetes, and how the interventions affect the development of cardiovascular disease and other complications of diabetes. The DPP group was highly diverse (45 percent from minority ethnic and racial groups), and DPPOS will compare outcomes for women and men, and by age and ethnicity. Renewed in FY 2009 for a second 5-year phase, the DPPOS will enable researchers to better determine the lasting benefits of the interventions to diabetes prevention and/or the delay of onset. In addition, NIH is pursuing translational research efforts to develop more cost-effective methods of achieving the lifestyle change that delayed or prevented diabetes in the DPP, and better methods to identify those with prediabetes. For example, one translational effort is using the YMCA to deliver a DPP lifestyle intervention; data from a recent pilot study suggest that using the YMCA may be a low-cost way to deliver a lifestyle intervention to large numbers of people in the United States. Many of these translational research studies focus on minority populations disproportionately burdened by type 2 diabetes and by obesity, a significant risk factor for type 2 diabetes.

→ For more information, see http://www.bsc.gwu.edu/dpp/protocol.htmlvdoc
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-09-176.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-06-532.html
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIDDK**, CDC, IHS, NEI, NHLBI, NIA, NICHD, NINR, OBSSR, ORWH)

Framework for Adherence Research: A Workshop: NIH organized and led an internal Adherence Research Network. The Network developed a formal evaluation plan for NIH's adherence research portfolio. As a part of the evaluation, NIH convened a think-tank style workshop, titled Framework for Adherence Research and Translation: A Blueprint for the Next Ten Years. The workshop was held March 9, 2008, in conjunction with the Third International Conference on HIV Treatment Adherence. The workshop participants discussed opportunities for future research on adherence as well as challenges to the field, including key methodological barriers that require a renewed public health effort to improve adherence to preventive and treatment regimens.

→ For more information, see http://obssr.od.nih.gov/scientific_areas/health_behaviour/adherence/index.aspx
→ (O) (**OBSSR**, NIMH)

Science of Dissemination and Implementation: More present than ever within the research community is the belief that to optimize public health we must not only understand how to create the best interventions, but how to best ensure that they are delivered effectively within clinical and community practice. This is the focus of dissemination and implementation research, and building this knowledge base is imperative to get the best return on decades of investment in biomedical, behavioral, and social sciences research. The goal of the January 28-29, 2009, NIH-sponsored conference on the Science of Dissemination and Implementation was to provide a venue for the research community to exchange ideas, explore contemporary topics, and identify concepts, methods, and strategies to build research and organizational capacity for dissemination and implementation science. The conference was intended to complement the program announcement, Dissemination and Implementation Research in Health, which supports innovative approaches to identifying, understanding, and overcoming barriers to the adoption, adaptation, implementation, and maintenance of evidence-based practices by health providers, insurers, policy makers, and the public, and is a follow-up to an earlier conference, Building the Science of Dissemination and Implementation in the Service of Public Health.

→ For more information, see http://obssr.od.nih.gov/funding_opportunities/foas/index.aspx
→ For more information, see http://obssr.od.nih.gov/news_and_events/conferences_and_workshops/DI2009/index.html
→ (E) (**OBSSR**, FIC, NCI, NHLBI, NIDA, NIDCD, NIDCR, NIMH, NINR, ODP/ODS)

Oversight of Genetic Technologies: In its April 2008 report, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) identified gaps in the oversight of genetic testing and critical steps that should be taken to address them. The five key gaps in existing policy were: (1) regulations governing clinical laboratory quality; (2) oversight of the clinical validity of genetic tests; (3) transparency of genetic testing; (4) the level of current knowledge about the clinical usefulness of genetic tests; and (5) the ability of health professionals, the public health community, patients, and consumers to use these new tests effectively. Most immediately, SACGHS recommended the creation of a national registry of laboratory-developed tests that also would contain information about the tests' complexity and clinical validity and utility.

→ For more information, see http://oba.od.nih.gov/policy/policy_issues.html#CRP_004
→ (O) (**OSP/OBA**, ATSDR)

Research Training for Clinicians in Practice-Based Research Networks Yields Results: When NIH awarded 6 7-year grants to establish 3 dental practice-based research networks (PBRNs), its aim was to assemble teams of practicing dentists to investigate with greater scientific rigor "everyday" issues in the delivery of oral health care. The impetus behind the networks was the frequent lack of research data to guide treatment decisions in the dentist's office. One of the key objectives to accomplishing the goal is providing the participating clinicians, many of whom have had no previous

research experience, with the training and education needed to conduct clinical research effectively. The PBRNs have developed multiple methods of delivering research training to practicing clinicians, including training in research methods, protection of human participants, good clinical practice, research protocol development, and interpretation of research results. Descriptions of the training programs have been reported in national journals, and a collaboratively written chapter recently was accepted for publication in a textbook on PBRNs. The real proof of the value of research training, of course, is whether research relevant to clinical practice is occurring—yes it is. Over the course of the grant period, the networks each will complete approximately 15 to 20 short studies. In early 2009 almost 90 study concepts had been approved, more than 20 were underway, and several had been completed and reported. The citations below are limited to those that deal with research training.

- → DeRouen TA, et al. *J Am Dent Assoc* 2008;139(3):339-45. PMID: 18310739.
  Gilbert GH, et al. *J Am Dent Assoc* 2008;139(1):74-81. PMID: 18167389.
- → For more information, see http://www.nidcr.nih.gov/Research/DER/ClinicalResearch/DentalPracticeBasedResearchNetworks.htm
- → This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- → (E) (**NIDCR**)

Disseminating Evidence-Based Health Information on Diabetes and Digestive and Kidney Diseases: The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational materials on diabetes and kidney disease, respectively. For example, the NDEP encourages people to take "small steps" to prevent type 2 diabetes. The NDEP also promotes the importance of comprehensive diabetes control in its "Control Your Diabetes. For Life" educational campaign. The NKDEP encourages African American families to discuss kidney disease at family reunions, and also provides tools and resources for health care providers to help coordinate care and improve patient outcomes for kidney disease. Both programs tailor materials for minority groups at high risk. Information Clearinghouses also provide key health information for patients, health care professionals, and the general public. A recent campaign highlighted the importance of using accurate methods to test hemoglobin A1c in people with diabetes who have sickle cell trait or other inherited hemoglobin variants. Other recent campaigns raised awareness of celiac disease and interstitial cystitis. The Weight-Control Information Network provides up-to-date, science-based information on weight control, obesity, physical activity, and related nutritional issues.

- → For more information, see http://www2.niddk.nih.gov/HealthEducation/
- → For more information, see http://ndep.nih.gov/
- → For more information, see http://nkdep.nih.gov/
- → For more information, see http://win.niddk.nih.gov/
- → This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- → (E) (**NIDDK**, CDC)

Getting Proven Treatments into the Criminal Justice System: Unfortunately, most inmates in need of substance abuse treatment do not receive it while in prison and, upon their release, continue a vicious cycle of drug use and crime. In response, NIH—along with multiple Federal agencies and health and social service professionals—is working systematically to move science-based treatment interventions into the criminal justice system, where they can have a major impact. In a Delaware Work Release study, those who participated in prison-based treatment followed by aftercare were 7 times more likely to be drug free after 3 years than those who received no treatment. Other research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) affirms the critical need for prisoners to receive effective substance abuse treatment while incarcerated and during their re-entry into the community. A recent randomized clinical trial found that prisoners who began methadone maintenance treatment in prison were significantly more likely after 12 months post-release to continue treatment and decrease drug use and criminal activity than a

counseling-only group. A related issue for this population is heightened HIV risk—the U.S. prison system also being where many inmates first receive HIV testing and initiate treatment. However, only a nominal percentage continues this treatment following release. New research shows that simply providing formal assistance in filing the paperwork for antiretroviral treatment medications can promote greater continuity of HIV pharmacotherapy among released inmates. Gaining insight into ways to reduce drug use and criminal recidivism—including among adolescents for whom the same issues apply—as well as limit HIV spread in communities means huge economic and social cost savings.

→ Baillargeon J, et al. *JAMA* 2009;301(8):848-57. PMID: 19244192.
Chandler RK, et al. *JAMA* 2009;301(2):183-90. PMID: 19141766. PMCID: PMC2681083.
Kinlock TW, et al. *J Subst Abuse Treat* 2009;37(3):277-85. PMID: 19339140. PMCID: PMC2803487.
Martin SS, et al. *Prison J* 1999;79(3):294-320.
→ For more information, see http://www.cjdats.org/
→ For more information, see http://www.drugabuse.gov/Blending/
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIDA**) (GPRA)

Understanding and Promoting Health Literacy: Low health literacy is a widespread problem, affecting more than 90 million adults in the United States, where 43 percent of adults demonstrate only the most basic or below-basic levels of prose literacy. Low health literacy results in patients' inadequate engagement in decisions regarding their health care and can hinder their ability to realize the benefits of health care advances. Research has linked low or limited health literacy with such adverse outcomes as poorer self-management of chronic diseases, fewer healthy behaviors, higher rates of hospitalizations, and overall poorer health outcomes. An NIH program announcement supports research that increases our understanding of the health literacy problem and its relationship to health disparities as well as the development of interventions to overcome the adverse consequences of low health literacy. In December 2008, a grantee meeting was convened to provide a venue for NIH-funded scientists conducting health literacy research to discuss lessons learned about health literacy-related topics, including measurement and methodology, actionable research (e.g., plain language, dissemination), and special populations (e.g., cognition, culture, and socioeconomic status). NIH is planning a fall workshop to highlight the state-of-the-science and to inform directions for reissuing the funding opportunity announcement in 2010.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-020.html
→ For more information, see http://obssr.od.nih.gov/scientific_areas/social_culture_factors_in_health/health_literacy/index.aspx
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**OBSSR**, AHRQ, NCI, NHLBI, NIA, NIBIB, NICHD, NIDCD, NIDCR, NIEHS, NIMH, NINR, NLM)

Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer Care: The purpose of the Cancer Research Network (CRN) is to enhance research on cancer epidemiology, prevention, early detection, and control in the context of health care delivery systems. CRN combines established research groups affiliated with 14 health care delivery organizations that provide comprehensive care to a racially and ethnically diverse population of nearly 11 million individuals. CRN has developed strong research capabilities in several areas: developing and applying innovative methods to collect and interpret data from both conventional and electronic medical records systems; assembling large samples of patients with documentation of patient characteristics and longitudinal data on receipt of health services and clinical and quality-of-life outcomes; collecting and integrating complex data from patients, providers, and organizations to examine issues in health care delivery from multiple perspectives; quantifying the effect of key factors in the delivery process that may determine quality and outcomes of care; and conducting studies on behavioral and systems-based interventions to improve the delivery of care in community-based health care delivery systems. The Breast Cancer Surveillance

Consortium (BCSC) is a research resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. The BCSC is a collaborative network of seven mammography registries with linkages to tumor and/or pathology registries. The Consortium's database contains information on 7,521,000 mammographic examinations, 2,017,869 women, and 86,700 cancer cases.

→ For more information, see http://crn.cancer.gov
→ For more information, see http://breastscreening.cancer.gov/
→ This example also appears in Chapter 2: *Cancer*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**NCI**)

Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging: NIH supports 13 Roybal Centers whose objective is to improve the health, quality of life, and productivity of middle-aged and older people by facilitating translation of basic behavioral and social science to practical outcomes by developing new technologies and stimulating new "use-inspired" basic research in the behavioral and social sciences. Roybal investigators have made several key discoveries. For example: One Center has developed tools and technologies for identifying older adults at risk for automobile crash involvement, and is working with industry partners to develop and disseminate products based on these tools. Another Center has developed two evidence-based interventions from its in-depth work on physical activity for older adults. One program, Fit and Strong!, is targeted to older adults with lower extremity osteoarthritis, and one is targeted to older adults with developmental/intellectual disabilities (primarily Down syndrome). A Roybal investigator has developed instruments for self-efficacy appropriate for use with older adults with developmental/intellectual disabilities; these have been adopted internationally. Finally, a Center has developed a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Other companies have used this model to develop related products, and the model has spurred several new grant-funded research projects, including the development of a new medication tracker for older adults.

→ For more information, see http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/roybals.htm
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NIA**)

Genomic Medicine: One of the promises of the Human Genome Project is the personalization of medicine. The time rapidly is approaching when health care providers will be able to use information about each person's unique genetic makeup to develop individualized strategies for detecting, treating, and, ultimately, preventing disease. A number of initiatives are underway to explore this area, including the Multiplex Initiative, the Surgeon General's Family History Initiative, and the ClinSeq project. The Multiplex Initiative, a collaboration between NIH researchers, the Group Health Cooperative in Seattle, and the Henry Ford Health System in Detroit, studied the interest levels of healthy young adults in receiving genetic testing for eight common conditions. The purpose was to understand better how patients respond to the results of genetic tests. The U.S Surgeon General's Family History online tool, created through a collaborative effort involving the Office of the Surgeon General, NIH, the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, and the Health Resources and Services Administration, allows people to record health conditions that have affected their relatives. The tool uses a three-generation pedigree to organize family health information in a format that people can easily share with their health care providers and other family members. Such information can lead to more proactive strategies for preventing disease and improving health. Finally, NIH researchers and their collaborators are enrolling volunteers in the ClinSeq project, which is piloting large-scale medical sequencing in a clinical setting, with a focus on cardiovascular disease.

→ Guttmacher AE, et al. *N Engl J Med* 2004;351(22):2333-6. PMID: 15564550.
→ For more information, see http://www.multiplex.nih.gov
→ For more information, see http://www.genome.gov/25521052
→ For more information, see http://www.hhs.gov/familyhistory
→ For more information, see https://familyhistory.hhs.gov
→ For more information, see http://www.genome.gov/20519355
→ This example also appears in Chapter 3: *Genomics*
→ (E, I) (**NHGRI**)

NIH and Comparative Effectiveness Research (CER): CER is the conduct and synthesis of research comparing the benefits and harms of different interventions to prevent, diagnose, treat, and monitor health conditions in real-world settings. (For the full HHS definition of CER, see *Comparing the Effectiveness of Different Therapies or Strategies* in the section of Chapter 3 on Clinical and Translational Research.) NIH has a long history of supporting landmark CER studies and of supporting CER research that challenges existing standards of clinical practice. NIH was awarded $400 million of the $1.1 billion allocated under auspices of the American Recovery and Reinvestment Act of 2009 for CER. An NIH "CER Coordinating Committee" was initiated to ensure optimal use of the stimulus funds, to make funding recommendations to the NIH Director, and to develop a long-term CER research plan for the future. The agency is working collaboratively with sister agencies (AHRQ, FDA, VA, etc.), is represented on the "Federal Coordinating Council for CER" (together with representatives from 15 Federal agencies and offices), and has consulted with the IOM regarding the drafting of its report on initial national priorities for CER. NIH plans to obligate the $400 million to advance CER via "Challenge Grants," "Grand Opportunity Grants," expansion of scope of research, etc. The agency will further ramp up capacity by investing in development of innovative trial design for conducting CER, in advancing statistical and modeling approaches capable of mining multidimensional databases, in undertaking planning studies to support large-scale trials to speed critical breakthroughs, and in forging the unique infrastructure capable of supporting the CER studies of tomorrow. These investments will generate CER findings of public health significance, high relevance to clinical medicine, and scientific excellence.

→ For more information, see http://www.iom.edu/
→ For more information, see http://www.hhs.gov/recovery/programs/os/cerbios.html
→ (O) (**OSP/OSPA**, DPCPSI, NCCAM, NCI, NCMHD, NCRR, NHLBI, NIA, NIBIB, NIDDK, NIMH, NINDS, ODP)

Collaboration, Education, and Genetic Test Translation Program for Rare Diseases (CETT): This research and education project was developed to make available genetic tests to patients from CLIA-certified laboratories. The vast majority of the known rare diseases are genetic disorders, thus genetic testing can be an essential part of the diagnosis and treatment continuum for rare diseases. The CETT program is a pilot program to translate new genetic tests from research in gene discovery to clinical practice and to meet an unfulfilled need for many rare diseases for which research did not translate to the development of a clinical diagnostic test. The mission of ORDR includes promoting the diagnosis of rare diseases and facilitating education in rare diseases. The CETT program encourages clinical laboratory and research collaborations, and supports the electronic collection of genetic and clinical data in public databases to leverage the information into new research and new treatments. During this pilot, the CETT program has supported the development of 34 genetic tests representing 67 diseases and 89 genes. The CETT Program also has piloted the development of educational materials about new test development for families and clinicians through the collaboration with advocacy and clinician experts in rare diseases and now is piloting the collection of de-identified clinical and genetic mutation information to be accessible publicly for the clinical and research community through partnership with NIH's National Center for Biotechnology Information. Tests put into development include DNM2 Centronuclear Myopathy, ROR2 Robinow Syndrome, ASPM, CDK5RAP2, CENPOJ, and MCPH1 for Autosomal Recessive Primary Microcephaly (University of Chicago); and ATPIA3 Rapid-Onset Dystonia Parkinsonism (Neurogenetics DNA Diagnostic Lab in

Boston). Other tests put into development earlier include Urea Cycle Disorders (Baylor College of Medicine); Inclusion Body Myopathy Associated with Paget Disease and/or Frontotemporal Dementia (University of California at Irvine); and Duchenne Muscular Dystrophy and Becker Muscular Dystrophy (Emory University).

→ For more information, see http://rarediseases.info.nih.gov/cettprogram/default.aspx
→ (O) (**ODP/ORDR**, NLM)

Translating CAM Research Results into Clinical Practice: Results from a National Survey of Physicians and CAM Providers: In an initial investigation of the potential for information from complementary and alternative medicine (CAM) research to influence clinical practice, a 2007 national survey asked acupuncturists, naturopaths, internists, and rheumatologists about their awareness of CAM clinical trials, their ability to interpret research results, and their use of research evidence in decisionmaking. The survey focused on awareness of two major NIH-funded clinical trials that studied acupuncture or glucosamine/chondroitin for osteoarthritis of the knee. According to the survey, more than half (59 percent) of the 1,561 respondents were aware of at least 1 of the 2 clinical trials, but only 23 percent were aware of both trials. A majority of respondents said they were "moderately confident" in their ability to interpret research literature; few—20 percent of acupuncturists, 25 percent of naturopaths, 17 percent of internists, and 33 percent of rheumatologists—said they were "very confident." All groups regarded clinical experience as "very important" in their decisionmaking, although CAM providers were more likely to rate it "most important." CAM providers were much more likely than physicians to rank research results as "least important," whereas physicians were much more likely to rate patient preferences as least important. The results of the survey demonstrate that CAM research has the potential to make a difference in both conventional and alternative medicine clinical practice. Concerted efforts are recommended to better train all clinicians in interpretation and use of evidence from research studies, and to improve the dissemination of research results.

→ Tilburt JC, et al. *Arch Intern Med* 2009;169(7):670-7. PMID: 19364996.
→ For more information, see http://nccam.nih.gov/research/results/spotlight/041309.htm
→ (E) (**NCCAM**)

A Behavioral Intervention to Improve Obstetrical Care: Background: Implementation of evidence-based obstetrical practices remains a significant challenge. Effective strategies to disseminate and implement such practices are needed. Adopting new evidence-based clinical practices and adapting them to different countries requires careful planning and adjustment of existing models to local conditions. Use of evidence-based guidelines improves quality of care, the behavior of health care practitioners, and the health outcomes of patients. Advance: This research focused on evaluating an intervention to facilitate the adoption of evidence-based practices in Latin American maternity hospitals. Using a cluster-randomized controlled trial design, this research evaluated the behavior and attitudes of birth attendants with respect to two evidence-based recommendations for obstetrical practice: the selective use of episiotomy and active management of the third stage of labor. The intervention was associated with an increase in use of prophylactic oxytocin and a decrease in the use of episiotomy. The intervention also was associated with reductions in the rate of postpartum hemorrhage. Birth attendants' readiness to change also increased in the hospitals receiving the intervention. The effects on the use of episiotomy and prophylactic oxytocin were sustained 12 months after the end of the intervention. Significance: This study, supported by NIH's International Clinical Operational and Health Services Research Training Award, addresses an implementation barrier and highlights that the use of evidence-based guidelines can improve the quality of care and the behavior of health care practitioners.

→ Althabe F, et al. *N Engl J Med* 2008;358(18):1929-40. PMID: 18450604.
→ For more information, see http://content.nejm.org/cgi/content/abstract/358/18/1929
→ For more information, see http://www.fic.nih.gov/programs/training_grants/icohrta/
→ (E) (**FIC**)

The Spine Patient Outcomes Research Trial (SPORT) for Low Back Pain: Before SPORT, many people who had chronic low back pain were conflicted about whether to undergo surgery; some were not sure surgery was worth the risk, while others feared that delaying surgery might cause even more damage. In the past 4 years, SPORT demonstrated that, indeed, surgery is superior to nonoperative treatments for the 3 most common causes of severe low back pain: intervertebral disk herniation and lumbar spinal stenosis with or without degenerative spondylolisthesis (the slipping of vertebrae). However, people who have one of these conditions are not subjecting themselves to further harm if they adopt a "wait-and-see" approach before committing to surgery. The benefits of surgery to correct spinal stenosis, for example, were apparent as early as 6 weeks after surgery. Those patients who had severe slippage and discomfort due to lumbar spinal stenosis with degenerative spondylolisthesis seemed to benefit the most. Although people who did not have surgery reported some improvement 2 years into the study, those who had surgery seemed to be doing considerably better. Additionally, SPORT showed that combining two surgical procedures—decompressive laminectomy and fusion—did not help patients who had lumbar spinal stenosis without degenerative spondylolisthesis any more than decompressive laminectomy alone did. The findings regarding intervertebral disk herniation equally were meaningful. Two years after surgery, patients who had surgery for a herniated upper lumbar disk felt significantly better than those who had a lower disk repaired. Although more costly than nonoperative approaches, such as medications and physical therapy, lumbar diskectomy is a cost-effective treatment, regardless of whether the damaged disk is in the upper or lower portion of the lumbar spine.

→ Lurie JD, et al. *J Bone Joint Surg Am* 2008;90(9):1811-9. PMID: 18762639. PMCID: PMC2657310.
Tosteson AN, et al. *Ann Intern Med* 2008;149(12):845-53. PMID: 19075203. PMCID: PMC2658642.
Tosteson AN, et al. *Spine* 2008;33(19):2108-15. PMID: 18777603.
Weinstein JN, et al. *Spine* 2008;33(25):2789-800. PMID: 19018250. PMCID: PMC2756172.
Weinstein JN, et al. *N Engl J Med* 2007;356(22):2257-70. PMID: 17538085. PMCID: PMC2553804.
Weinstein JN, et al. *N Engl J Med* 2008;358(8):794-810. PMID: 18287602. PMCID: PMC2576513.
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIAMS**, CDC/NIOSH, ORWH)

Bolstering the Research Continuum

Extramural Construction Program Expands Research Capacity: The American Recovery and Reinvestment Act (ARRA) provided $1 billion to NIH for the Extramural Construction program. The program will build capacity to conduct biomedical and behavioral research by supporting the costs of improving non-Federal basic research, clinical research, and animal facilities to meet the research, research training, or research support needs of institutions. One component of the program, the Extramural Research Improvement Program, awards grants to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities for biomedical and behavioral research. Another component of the program, the Core Facility Renovation, Repair, and Improvement activity, awards grants to public and nonprofit private entities to renovate, repair, or improve core facilities. A core facility is a centralized shared resource that provides access to instruments or technologies or services, as well as expert consultation to investigators supported by the core. Institutions apply for construction grants by submitting applications, which are selected using NIH's standard, competitive, peer-reviewed process. Funding decisions are based on the scientific and technical merit of the application as determined by first and second level of peer review, the availability of funds, the relevance of the application to NIH program priorities, the national geographic distribution of awards, and the priorities specified in the ARRA, such as energy efficiency and job creation. The objective of the ARRA Extramural Construction program aligns with the objective of the existing Research Facilities Improvement Program, which is also administered by NIH.

→ For more information, see http://www.ncrr.nih.gov/recovery/construction

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NCRR**) (ARRA)

ARRA-Funding Expands Research Capabilities: NCRR is using its ARRA funds designated for scientific research to accelerate the Center's research priorities and support research, resources, tools, and training to help researchers funded by NIH transform basic discoveries into improved human health. In contrast to most of the NIH ICs that fund primarily Research Project Grants (i.e., R01s), NCRR primarily supports large Center programs that build research capacity and offer training and career development. Consistent with NCRR's research portfolio, a few previously reviewed Research Project Grants (R01s and R21s) are being awarded with ARRA funds. Through competitive revision awards, NCRR is encouraging NIH-funded researchers (primarily supported by other NIH ICs) to leverage the resources, expertise, and infrastructure of NCRR centers and Center-like programs. To further advance the scientific progress of NCRR programs, administrative supplements are being awarded to: advance translational (pre- and post-clinical) research, achieve CTSA consortium strategic goals, enhance NCRR pilot project mechanisms, promote collaborative community engagement research, improve research workforce development, and strengthen science education and dissemination. A new ARRA-supported initiative will develop infrastructure to connect people and resources across the Nation and promote interdisciplinary collaborations and scientific exchange. Additional ARRA funding is supporting NIH-led activities such as the Challenge Grants and the Summer Research Experiences for Students and Science Educators. From the beginning of the ARRA-funding strategy development, NCRR leadership decided to align its ARRA activities broadly with the goals and objectives of the NCRR 2009-2013 Strategic Plan.

→ For more information, see http://www.ncrr.nih.gov/recovery
→ For more information, see http://www.ncrr.nih.gov/strategic_plan/implementation/
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Technology Development*
→ (E) (**NCRR**) (ARRA)

Shared Instrumentation Grant and High-End Instrumentation Programs: The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the $100,000-$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the $750,000-$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located at core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2008, the SIG program funded a total of 82 grants for $30,623,406; the HEI funded a total of 20 awards for $33,309,434. In FY 2009, NIH received $300 million in ARRA funding to provide shared instrumentation to extramural researchers through the SIG and HEI programs. To best serve the needs of NIH-supported investigators, the range of HEI awards funded by ARRA was expanded and now is $600,000 to $8 million.

→ For more information, see http://www.ncrr.nih.gov/btinstruments
→ For more information, see http://www.ncrr.nih.gov/recovery
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NCRR**) (ARRA)

Using Systems Science Methodologies to Protect and Improve Population Health: Solutions to complex problems, such as chronic disease, require approaches that can address a broad range of factors within a single framework—from genetic to environmental, cellular to behavioral, and biological to social. In May 2007, NIH sponsored a conference, Complex Approaches to Population Health, at the University of Michigan. This well-attended (300 persons) conference brought computational/mathematical modelers together with behavioral and social scientists to discuss longstanding problems in health that might be addressed with these modeling methods. A primary purpose of the conference was to raise awareness of systems science methodologies as a means for addressing population health problems. Informed by the 2007 meeting, NIH issued the initiative PAR-08-224, Using Systems Science Methodologies to Protect and Improve Population Health, in August 2008. The initiative solicits R21 grant applications that propose using systems science methodologies to address policy resistant health problems. There are three application receipt dates per year through 2011.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-224.html
→ (E) (**OBSSR**, FIC, NCCAM, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIDCR, NIEHS, NIMH, ODP, ODP/ODS)

Blueprint Interdisciplinary Research Training: Under the auspices of the NIH Blueprint, interdisciplinary training programs have been established in computational neuroscience, neuroimaging, and translational research in the neurobiology of disease.

- The computational neuroscience programs seek to attract undergraduate and predoctoral students from the physical, mathematical, and engineering sciences to neuroscience research, and to expand the training of neuroscience students in quantitative sciences. Students learn how to develop models of neural systems or processes, test them experimentally, and then use experimental data to refine the models.
- The neuroimaging programs support predoctoral students and summer research intensives and provide comprehensive training in the breadth of imaging techniques and their application to neuroscientific questions. The goal of these programs is to train the next generation of neuroimaging researchers in the limitations, advantages, and underlying principles of currently available neuroimaging modalities.
- The translational research programs support students at multiple stages of their careers. The programs are designed to cross-train students in basic and clinical neuroscience, focusing not on specific diseases but on the biological mechanisms that are shared across diseases.

These Blueprint training programs are successfully seeding the field of neuroscience with highly qualified graduate students, postdoctoral fellows, and faculty.

→ For more information, see http://neuroscienceblueprint.nih.gov/neuroscience_resources/training.htm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Research Training and Career Development*
→ (E) (**NIH Blueprint**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

Recruiting for HIV Research Using Mobile Vaccine Units: Evaluating the safety of candidate vaccines and treatments in humans depends on trust and partnership among scientists, clinicians, and study volunteers. NIH is reaching out to District of Columbia (DC)-area communities to raise awareness among diverse groups about HIV/AIDS. The mobile clinic is an extension of the vaccine clinic of the NIH Vaccine Research Center (VRC). The mobile clinic facilitates collaboration among scientists, clinicians, and study volunteers by raising awareness about HIV vaccines and by improving access for volunteers. With its new mobile clinic, the VRC enhances this vital collaboration by improving access for people in the DC metropolitan area who volunteer for clinical research studies to help find vaccines for HIV/AIDS and other infectious diseases. The mobile clinic can expand NIH outreach and recruitment efforts to neighborhoods in Baltimore and Frederick, Maryland, as well as DC and its suburban neighbors. The unit made its first

community appearance in June 15, 2008, at the 33rd annual Capital Pride Festival (a signature event held by the lesbian/gay/bisexual/transgender community).

→ For more information, see http://nihrecord.od.nih.gov/newsletters/2008/07_25_2008/story4.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (I) (**NIAID**)

Stimulating Transformative Research in HIV/AIDS: In recent years, widespread public education campaigns in the United States have fueled progress in reducing HIV/AIDS transmission that occurs through the sharing of injection equipment among drug users. However, transmission through high-risk sexual contact is on the rise—these behaviors often are exacerbated by substance abuse and ensuing altered judgment. To achieve a more comprehensive approach to this problem, NIH initiated its Avant-Garde Award series in 2008, with the goal of stimulating high-impact research from varied scientific disciplines to pave new avenues of treatment for HIV disease and prevention of new HIV infections among drug abusers. This award, modeled after NIH's Pioneer Award, provides funds of up $0.5 million per year for 5 years and uses interviews with prospective candidates to more fully discern the scientist's and project's potential. One exemplary awardee is evaluating the effectiveness of expanding highly active antiretroviral treatment (HAART) coverage among injection drug users as a population-level HIV prevention strategy. A second is focusing on the ability of HIV to hijack key proteins involved in the regulation of host cell gene expression. A second initiative, the AIDS-Science Track Award for Research Transition (A-START), facilitates the entry of newly independent and early career investigators into the area of drug abuse and HIV/AIDS, an identified area of research need. Examples of projects supported through this mechanism include research on: (1) statistical models to explain ethnic disparities in HIV/AIDS among drug users, and (2) effects of morphine on immune responses to a candidate HIV vaccine in a primate model.

→ For more information, see http://www.cdc.gov/hiv/topics/surveillance/incidence.htm
→ For more information, see http://www.drugabuse.gov/about/organization/arp
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIDA**)

Institutional Development Award (IDeA) Program: The NIH IDeA program fosters health-related research and improves the competitiveness of investigators in 23 states and Puerto Rico with historically low NIH funding. The IDeA program supports multidisciplinary centers and statewide collaborative partnerships that increase institutions' capacity to conduct cutting-edge biomedical research. IDeA supports faculty development and enhancement of research infrastructure at institutions and also promotes collaborative community-based research, particularly in minority communities and other medically underserved communities where health disparities persist. The IDeA program supports the IDeANet initiative, which is expanding access to high-performance computational resources for data-intensive science applications and providing bioinformatics software tools and training to investigators. IDeANet began with the Lariat Networking Project, a pilot program that has enabled connectivity in six IDeA states in the Northwest (Alaska, Hawaii, Idaho, Montana, Nevada, and Wyoming) in partnership with the University of Washington and the University of California, San Diego. The Louisiana Optical Network Initiative (LONI) followed, supporting high bandwidth connectivity in Louisiana and Mississippi. Recently, five IDeA states have formed the North East Cyberinfrastructure Consortium (Delaware, Maine, New Hampshire, Rhode Island, and Vermont). IDeANet ultimately will enable all institutions in the IDeA program to engage in national and international collaborations.

→ For more information, see http://www.ncrr.nih.gov/riidea
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NCRR**) (GPRA)

Research Centers in Minority Institutions (RCMI): The RCMI program has developed and enhanced the research infrastructure of minority-serving institutions by expanding human and physical resources for conducting basic, clinical, and translational research. It began in 1985 in response to congressional report language (House Report 98-911, on the Labor, Health and Human Services, and Education and Related Agencies Appropriation Bill for FY 1985; July 26, 1984; pages 78-79), directing funds to "establish research centers in those predominantly minority institutions which offer doctoral degrees in the health professions or the sciences related to health." The RCMI program has provided resources to acquire advanced instrumentation, renovate laboratory facilities, and improve research infrastructure. Additionally, it has enhanced faculty development, funded pilot projects, and supported core facilities. Because many RCMI investigators study diseases that disproportionately affect minorities, NIH support has brought more minority scientists into mainstream research and enhanced biomedical research focused on improving the health of racial and ethnic minorities and other medically underserved populations. The RCMI program includes various types of awards to help improve research capacity and reduce health disparities. For example, the RCMI Translational Research Network has fostered collaboration among researchers, developed and shared practices in disease prevention in local communities, and funded informatics tools for managing clinical research data. The RCMI program also has supported Clinical Research Education and Career Development awards that provide didactic training and mentor clinical research experiences to develop independent researchers.

→ For more information, see http://www.ncrr.nih.gov/ircmi
→ For more information, see http://www.ncrr.nih.gov/rtrn
→ For more information, see http://www.ncrr.nih.gov/crecd
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NCRR**, NCMHD, NHLBI, NIA, NIAMS, NICHD, NIDA, NIDDK, NIMH)

Research Training and Career Development for Veterinarians in Translational Biomedical Research: Two recent reports from the National Academies, *National Need and Priorities for Veterinarians in Biomedical Research* and *Critical Needs for Research in Veterinary Science*, have confirmed the shortage of veterinarians involved in biomedical research. To address the shortage, NIH provides research training awards ("T" Awards) in biomedical research specifically for veterinarians and veterinary students. During FY 2008, more than 75 veterinarians received research training under the "T" mechanism. The mentored Career Development Awards ("K" Awards) to veterinarians serve as a bridge for postdoctoral fellows to become independent investigators. In FY 2008, 22 career development "K" awards were made to young veterinary investigators to increase the number of biomedical researchers with this expertise. Additionally, another initiative encourages the training of veterinarians in nonhuman primate clinical medicine at NIH-supported primate centers to address the shortage of clinical veterinary support for research primate colonies.

→ For more information, see http://www.ncrr.nih.gov/career_development_opportunities/individual_training_grants/
→ This example also appears in Chapter 3: *Research Training and Career Development*
→ (E) (**NCRR**)

Center for Human Immunology, Autoimmunity, and Inflammation: The Center for Human Immunology, Autoimmunity, and Inflammation (CHI) is a new trans-NIH intramural initiative designed to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiologies, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease. The Center provides unique specific technologies often unavailable to individual laboratories because of cost, complexity, and novelty. The core of CHI is made up of three technology centers. The first center features assays of immune cells and their products, based mainly on a technique known as flow cytometry and similar emerging techniques. The second center contains high-throughput systems technologies, involving the use of new methods for large-scale examination of genes, proteins, enzymes, and/or lipids. It also features advanced biostatical

and computer modeling methods for mining these diverse data sets, thereby providing for a deeper understanding of immune function and pathology. The third center is based in protocol development, with staff dedicated to producing methods that efficiently translate to the clinic while considering all of the ethical and regulatory requirements for human research.

→ For more information, see http://www.nhlbi.nih.gov/resources/chi/index.htm
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Technology Development*
→ (I) (**NIAMS**, NCI, NHLBI, NIAID, NICHD, NIDDK, NINDS)

Translational Research at the Aging/Cancer Interface: The NIH Translational Research at the Aging/Cancer Interface initiative was established in 2008 to enhance research in the overlapping areas of human aging and cancer by (1) integrating knowledge of basic processes in cancer biology and aging into clinical care of older patients with cancer ("bench to bedside"), and (2) exploring clinical observations from the patient care setting at more basic and molecular levels ("bedside to bench"). Research supported by this initiative holds potential for improving prevention, diagnosis, and disease management; improving the health and well-being of older adults at risk for or diagnosed with cancer; and decreasing the functional impairment and morbidity associated with cancer in this population.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-230.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-231.html
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NIA**)

Public Trust Initiative: The NIH Public Trust Initiative (PTI), in partnership with the NIH Roadmap for Research, seeks to provide an inventory of activities that NIH and its individual Institutes and Centers are engaged in that involve public constituents, and that are intended to inform, educate, hear from, and serve the public. In 2008, NIH extended a new opportunity in community-based research under the PTI, the Partners in Research initiative (PIR). The PIR provides a unique opportunity for scientists to team up with community organizations to address the practical questions surrounding the development of true partnerships between researchers and the public. The goals of these partnerships are to: facilitate discussion of the health care needs and interests of the community; develop and implement research programs that address these needs; study methods to engage and inform the public regarding health science; improve public understanding of the benefits of publicly funded research; and communicate the results of this research. NIH received more than 200 applications in response to this opportunity, and a total of 37 projects were funded in 2008. On October 26-27, 2009, NIH convened a PIR workshop to examine the experiences of those participating in the PIR program. Participants discussed various aspects of the PIR program, including, for example, building partnerships, establishing criteria for a good partnership, and identifying challenges to this type of research.

→ For more information, see http://publictrust.nih.gov
→ (E) (**NINR, NICHD**, CC, FIC, NCI, NCRR, NIAID, NIDCR, NIGMS, OCPL, OIR, OSP/OBA)

Molecular Therapy Centers for Cystic Fibrosis and Other Genetic Metabolic Diseases: NIH is working to develop new approaches to treating serious, chronic, genetic diseases like cystic fibrosis and mucopolysaccharidosis. For example, the Gene Therapy and Cystic Fibrosis Centers Program currently supports Molecular Therapy Centers and a Cystic Fibrosis Research and Translation Core Center. Molecular Therapy Centers provide shared resources to a group of investigators to facilitate development of molecular therapies for the treatment of cystic fibrosis and other genetic metabolic diseases, like so-called lysosomal storage disorders such as mucopolysaccharidosis I. The Cystic Fibrosis Research and Translation Core Center provides resources and supports research on many aspects of the pathogenesis and treatment of cystic fibrosis. These centers have made important strides in recent years, including the study of promising

candidate therapeutics. One of these, PTC124, is designed to overcome a mutation in the cystic fibrosis gene that otherwise yields a truncated, inactive cystic fibrosis protein. Other centers are screening libraries of compounds for other agents that might be safe and effective therapeutics for cystic fibrosis and other metabolic diseases.

→ Du M, et al. *Proc Natl Acad Sci U S A* 2008;105(6):2064-9.PMID: 18272502. PMCID: PMC2538881. Galietta LJV, et al. *FEBS Letters* 2001;499(3):220-4. PMID: 11423120.
→ For more information, see http://www2.niddk.nih.gov/Research/ScientificAreas/GeneticGeneTherapy/GCTR.htm
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDDK**)

Training Activities of the Clinical and Translational Science Award Program: Clinical research requires unique skills in addition to those needed to care for patients, so academic health centers must equip members of clinical research teams with the special training and experience they need to succeed. NIH expanded its clinical research training programs through Roadmap T32 and K12 programs that largely have been assimilated into Clinical and Translational Science Awards (CTSAs). Clinical research trainees learn the skills needed to cultivate multidisciplinary research team collaborations and design research projects to compete successfully for funding in a mentored environment. The CTSA training program already is providing more than 1,000 research training and career development opportunities in multiple individual disciplines. As mandated in Section 106 of the National Institutes of Health Reform Act of 2006 (Pub. L. No. 109-482), NIH will evaluate the outcomes and effectiveness of the CTSA training programs. The evaluation will include surveys of trainees, scholars, and mentors and will address pediatric clinical research training issues. In addition, the evaluation will conduct secondary analyses of pediatric clinical research training data collected by the CTSA program. This is part of a much larger comprehensive evaluation of the CTSA program as a whole. Each individual CTSA recipient also evaluates his or her own training activities, and the CTSA Education/Career Development Key Function Committee provides a forum in which best educational practices can be identified. The CTSA program was initiated in September 2006, so the long-term impact of the CTSA program will not be known for 7 or more years. However, short-term process milestones and intermediate outcomes are expected in 1 to 7 years. For example, the CTSA consortium defined training standards for core competencies in clinical and translational research. The consortium identified the skills, attitudes, and knowledge that investigators need to participate successfully in multidisciplinary teams of clinician-scientists.

→ For more information, see http://nihroadmap.nih.gov/clinicalresearch/overview-training.asp
→ For more information, see http://www.ctsaweb.org
→ For more information, see http://www.ncrr.nih.gov
→ This example also appears in Chapter 3: *Research Training and Career Development*
→ (E) (**NCRR**, Common Fund - all ICs participate)

Interdisciplinary Research Consortia Funded by the NIH Roadmap: One of the four main initiatives established by the NIH Roadmap's Interdisciplinary Research Work Group was a grant program to fund large-scale consortia to support interdisciplinary research. In total, NIH funded nine collaborative teams located across the United States. Each focuses on a particular health problem or process, including substance abuse and stress; obesity; developmental disorders; the process of aging; providing fertility options for cancer survivors; engineering healthy tissue to treat diabetes, heart disease and oral/craniofacial disorders; psychiatric disorders; drug/medications development; and genome engineering. The initial results suggest ways in which this team science approach helps to increase cooperation within and between academic institutions, as well as advancing the individual missions of NIH ICs.

→ For more information, see http://nihroadmap.nih.gov/interdisciplinary/
→ For more information, see http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp
→ For more information, see http://nihroadmap.nih.gov/interdisciplinary/members.asp

→ For more information, see http://nihroadmap.nih.gov/
→ This example also appears in Chapter 3: *Technology Development*
→ (E, O) (**NIDCR**)

Enhancing Behavioral and Social Sciences in Medical Education: In 2004, the Institute of Medicine (IOM) released its report on *Improving Medical Education: Enhancing the Behavioral and Social Science Content of Medical School Curricula*, which NIH funded. The report summarized how medical school curricula should be enhanced to address critical health issues faced in the United States today. One major finding was that approximately half of all causes of mortality in the United States are linked to social and behavioral factors such as smoking, diet, alcohol, sedentary lifestyle, and accidents. While generally it is recognized that biomedical research alone cannot address these issues, the IOM found that the curriculum in most U.S. medical schools does not provide sufficient teaching about these behavioral and social risk factors. In response to the IOM report, NIH issued a 2004 RFA and funded grants to nine medical schools to develop, pilot, and disseminate behavioral and social sciences modified curricula across the six domains identified by the IOM: (1) Mind-Body Interactions in Health and Disease, (2) Patient Behavior, (3) Physician Role and Behavior, (4) Physician-Patient Interactions, (5) Social and Cultural Issues in Health Care, and (6) Health Policy and Economics. Working in close collaboration, these medical schools are addressing how to incorporate behavioral and social sciences content throughout all 4 years of medical school in both the preclinical and clinical curricula. About 6,100 medical students will be affected by curricular innovations over the next 2 years of this 5-year collaborative effort.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-05-001.html
→ (E) (**OBSSR**, NCCAM, NCI, NHLBI, NIAMS, NICHD)

Clinical and Translational Science Award (CTSA) Program: The CTSA program is a partnership between NIH and a national consortium of 46 academic health centers and research institutions to build academic homes for clinical and translational research. By 2011, NIH expects to fund 60 CTSA institutions at a total cost of $500 million per year. The CTSA program is designed to translate more efficiently the rapidly evolving knowledge developed in basic biomedical research into treatments to improve human health. The CTSA institutions are designing clinical and research informatics tools, forging new partnerships with private and public health care organizations, expanding outreach to minority and medically underserved communities, and developing better designs for clinical trials. Additionally, the CTSAs are training the next generation of clinical and translational researchers to excel in interdisciplinary team science. Working together, the consortium is developing and disseminating best practices, policies, procedures, and other measures to advance collaborative clinical and translational research. At the same time, NIH is encouraging active collaboration among CTSAs and other NIH-funded programs and investigators to leverage program resources and increase efficiencies. The CTSA program is the primary initiative for addressing the NIH Roadmap for Medical Research theme to Re-Engineer the Clinical Research Enterprise.

→ For more information, see http://www.ncrr.nih.gov/ctsa
→ For more information, see http://www.ctsaweb.org
→ (E) (**NCRR**, Common Fund - all ICs participate)

Clinical and Translational Science Award (CTSA) Program Evaluation: NIH recognizes the importance of accountability and the need to evaluate and demonstrate progress toward meeting the ambitious goals of the CTSA program. For this reason, each CTSA grantee is required to conduct an institutional evaluation and to submit an annual status report to NIH. Institutional evaluators also participate in the CTSA consortium's Evaluation Key Function Committee, which provides an interactive forum to share and disseminate best practices and approaches to evaluating CTSA grantee programs. Additionally, NIH has hired external evaluators from Westat, a leading government services organization, to evaluate implementation of the CTSA program independently, to consider stakeholders' needs and

perceptions, and to identify barriers to and facilitators of progress. As data are collected and as the program continues to mature, evaluation efforts will capture long-term outcomes and the impact the CTSA program has had on transforming the discipline of clinical and translational research. NIH will ensure that program findings and outcomes are disseminated to stakeholders, including researchers, advocacy groups, and Congress.

→ For more information, see http://www.ctsaweb.org
→ For more information, see http://www.ncrr.nih.gov/ctsa/progress_report_2009
→ (E) (**NCRR**, Common Fund - all ICs participate)

Clinical and Translational Science Award (CTSA) Program Progress: Launched in 2006, NIH has made significant progress in building a national consortium for clinical and translational research. Since 2008, 22 new CTSAs joined the consortium, adding representation from eight new states, additional pediatric expertise, and greater informatics capabilities. At the national level, the CTSA consortium has identified five strategic goals: developing strategies and resources to move laboratory discoveries into early clinical testing (T1 translation), reducing complexities and improving ways clinical and translational research is conducted, enhancing training and career development of clinical and translational investigators, encouraging consortium-wide collaborations, and improving the health of communities across the nation—with an emphasis on community engagement and comparative effectiveness research. Working together, the consortium has made substantial progress in improving the management of clinical research, developing core competencies in clinical and translational science, and accelerating the dissemination of research findings into clinical practice. The momentum of the CTSA consortium continues to build as new connections are emerging rapidly within, across, and beyond the consortium. For example, CTSAs are connecting with the following NIH-funded institutions: Emory University (Atlanta, Georgia) is partnering with Morehouse School of Medicine; Vanderbilt University (Nashville, Tennessee) is partnering with Meharry Medical College; and Weill Cornell Medical College (New York, New York) is partnering with Hunter College.

→ For more information, see http://www.ncrr.nih.gov
→ For more information, see http://www.ctsaweb.org
→ For more information, see http://www.ncrr.nih.gov/ctsa/progress_report_2009
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NCRR**, Common Fund - all ICs participate)

Collaborative Community-Based Research: NIH is focusing on strategies and best practices for conducting collaborative community-based clinical and translational research, particularly in minority and other medically underserved communities where health disparities persist. Programs such as the Institutional Development Award (IDeA) are encouraging efforts to build and strengthen partnerships among government agencies, academic and private-sector organizations, community health providers, and organizations that also are working to improve community health outcomes. Translational, community-based research funded in several IDeA states, in both urban and rural settings, is focusing on:

- Enhancing recruitment and retention of research subjects through community buy-in
- Implementing practical and effective research protocols in community health care settings
- Developing versatile and sustainable core research infrastructure to encourage community participation and leverage existing resources

In addition, in FYs 2008 and 2009, NIH conducted workshops to gather specific recommendations from the community that are helping to shape future initiatives to enhance clinical and translational research in minority and other medically underserved communities. Workshop participants included other HHS-agencies such as AHRQ, CDC, the Indian Health Service, and HRSA.

→ For more information, see http://www.ncrr.nih.gov/research_infrastructure
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NCRR**)

Community-Based Participatory Research (CBPR): CBPR is an orientation to research that requires a collaborative approach to involve community stakeholders throughout all stages of research projects. This community input offers CBPR the potential to generate better-informed hypotheses, develop more effective interventions, and enhance the translation of research results into practice. NIH issued three funding opportunity announcements (FOAs) on CBPR in January 2008. One FOA, Community Participation in Research, solicits jointly conducted intervention research. The remaining FOAs, Community Participation Research Targeting the Medically Underserved, solicit jointly conducted research in medically underserved areas/populations; all three FOAs focus on health promotion, disease prevention, and health disparities. A corresponding technical assistance workshop, Leap into the Community, convened February 2008 and offered comprehensive instruction from NIH program and review officials on the CBPR approach and preparing responsive applications to the FOAs. Outreach and training activities on CBPR have included the creation of an educational brochure (November 2007); organization of two special sessions at annual scientific meetings for the Society of Behavioral Medicine and the American Sociological Association on the principles and efficacy of CBPR and showcasing successful NIH-funded research projects (March 2008 and August 2009, respectively); and planning of the 2009 NIH Summer Institute on Community-Based Participatory Research Targeting the Medically Underserved, which addresses essential issues inherent in conducting community-partnered research with medically underserved areas/populations (August 2009).

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-074.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-075.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-076.html
→ For more information, see http://obssr.od.nih.gov/scientific_areas/methodology/community_based_participatory_research/CBPR_TA_Wrkshp.aspx
→ For more information, see http://obssr.od.nih.gov/scientific_areas/methodology/community_based_participatory_research/CBPR_ASA.aspx
→ For more information, see http://conferences.thehillgroup.com/si2009/index.html
→ For more information, see http://obssr.od.nih.gov/scientific_areas/methodology/community_based_participatory_research/index.aspx
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**OBSSR**, CDC/NIOSH, NCI, NHLBI, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINR, ORWH)

Community Participation in Health Disparities Intervention Research Program: NIH supports the development, implementation, and evaluation of intervention research by using community-based participatory research (CBPR) principles and methods in targeting diseases of major public health importance in health disparity communities. This unique multiyear CBPR initiative promotes participatory research collaborations between scientific researchers and their community partners and will engage communities in all stages of the research process for a total of 11 years (3-year planning phase, 5-year intervention phase, and 3-year dissemination phase). The participatory partnerships formed between researchers and the community are expected to (1) transform the research questions from researcher to community-centered; (2) focus the research area, strategies, and methods to address those diseases and conditions of highest community interest and need; and (3) accelerate the identification and testing of interventions that are likely to make the largest difference in the health of the community. The CBPR initiative began in FY 2005 with the award of 25 3-year research planning grants. CBPR planning grantees conducted needs assessments, focus groups, and pilot intervention studies for addressing health disparities among health disparity populations in 20 states. In FY 2008, 40 5-year

intervention research grants focusing on diabetes, cancer, cardiovascular disease, substance abuse, and other diseases and conditions were awarded. This intervention phase will be followed by a competition for 3-year dissemination grants to be awarded in FY 2013. In May 2009, RFA MD-09-006, "Recovery Act Limited Competition: NCMHD Community Participation in Health Disparities Intervention Research Planning Phase," was issued for a 2-year planning research phase. Awards for this phase were made in FY 2009. Current CBPR pilot intervention research studies include:

- Suicide and alcohol use prevention among Alaska Native youth living in five communities in Alaska
- HIV/AIDS prevention among African Americans in North Carolina
- Obesity prevention using individual, family, and community-level interventions among Native Hawaiian and Pacific Islanders in Hawaii
- Diabetes prevention among Hispanic communities in border areas in Texas
- Hypertension prevention among Filipino Americans in New York City and New Jersey
- Cancer prevention among low-income Appalachian communities in Ohio by increasing colorectal cancer screening

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/rfa-md-07-003.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-09-006.html
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NCMHD**)

Testing for Reproductive Tumors in the National Toxicology Program's Carcinogenesis Bioassay: Perinatal Dosing: The National Toxicology Program (NTP) evaluates substances for a variety of health-related effects. Two-year studies in laboratory rodents remain the primary method by which chemicals or physical agents are identified as having the potential to be hazardous to humans. In 2006, NTP convened a workshop on Hormonally Induced Reproductive Tumors, Relevance of Rodent Bioassays to discuss the adequacy of rodent models used in the 2-year bioassay for detecting reproductive tumors. The workshop recommended that in utero and lactational exposures could be added to the chronic bioassay depending upon what is known about the mode of action. For detecting tumor types such as testicular germ cell tumors, this recommendation was especially strong. In utero and lactational exposures should be considered for mammary tumor studies if there are any developmental effects associated with a substance under study that involved endocrine tissues, steroid receptor binding, a change in mammary gland morphology, or altered timing of vaginal opening. NTP has conducted such perinatal exposures on cancer bioassays in the past, but only when there was special justification for such a design to be adopted. A new default design in which dosing will start in pregnancy and be continued throughout life or to the end of a 2-year period now has been adopted unless there is a good scientific reason not to undertake such a study. NTP has initiated studies to obtain data for constructing physiologically based pharmacokinetic (PBPK) models in rodents and nonhuman primates. It is planning studies to explore the long-term consequences of perinatal exposure to Bisphenol A to understand the potential impact to humans of the developmental changes reported in numerous laboratory animal studies. It is hoped that the PBPK models will link information from rodent studies with primate studies, and potentially with human outcomes.

→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
→ (O) (**NIEHS**)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists,

research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects adipose tissue and alters hormonal control of sexual maturation. Endocrine distruptors, irradiation, and psychosocial elements also will be studied for effects.

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→ For more information, see http://www.bcerc.org/
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIEHS**, NCI) (GPRA)

Cancer Health Disparities Research Programs and Initiatives: NIH has expanded research on the basic biologic factors of cancer disparities to provide a foundation for minimizing risk, identifying targets, developing preventive and therapeutic interventions, and understanding how genetic susceptibility may be influenced by social, economic, race/ethnicity, and geographic factors. Thus, the research programs involve multidisciplinary teams, which contribute to understanding the etiology of cancer and build prevention and intervention evidence-based models to eliminate cancer disparities. Several programs at NIH address disparities along the cancer continuum from prevention to survival.

- The trans-disciplinary Geographic Management Program (GMaP) pilot initiative builds regional networks to support research, training, and infrastructure to develop state-of-the-art networks/centers to ensure a continuous supply of high-quality human biospecimens from multi-ethnic communities.

- The Community Networks Program engages communities experiencing cancer disparities to design, test, and evaluate evidence-based strategies to address critical needs, such as access to screening, mentoring, and training; policy development; and community outreach and education.
- The Patient Navigation Research Program builds partnerships to ensure that racial/ethnic minorities and underserved populations with abnormal cancer screening results receive appropriate care.
- The Community Clinical Oncology Program is a network for conducting cancer prevention and treatment clinical trials by connecting academic centers with community physicians.
- The NIH Centers for Population Health and Health Disparities catalyze transdisciplinary research to improve the understanding of complex interactions of biological, social, cultural, environmental, and behavioral factors that contribute to health inequities, and to develop and implement novel intervention strategies that are multilevel and multifactorial.
- The Tobacco Research Network on Disparities' mission is to understand and address tobacco-related disparities by advancing the science, translating that scientific knowledge into practice, and informing public policy.
- The Centers of Excellence in Cancer Communication Research continue to use best practices in communication science to extend the reach of biomedical benefits equitably throughout the population.

→ For more information, see http://crchd.cancer.gov/
→ For more information, see http://crchd.cancer.gov/cnp/background.html
→ For more information, see http://crchd.cancer.gov/pnp/pnrp-index.html
→ For more information, see http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/index.html
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NCI**)

Collaborations Between Minority-Serving Institutions and Cancer Centers: The Minority Institution (MI)/Cancer Center (CC) Partnership (MI/CCP) is a flagship program that has been instrumental in establishing strong collaborations between minority-serving institutions (MSIs) and CCs. MI/CCP has fostered strong cancer research partnerships throughout the United States. This program established new cancer research curricula, recruited new faculty, increased awareness about health care disparities and cultural sensitivities, and developed programs and outreach efforts in educating underserved communities. The MI/CCP has provided research education and training to individuals at all levels including postdoctoral fellows, medical students, graduate students, students at master's level, and baccalaureate and high school students. Establishing new collaborations and partnerships in communities has been a hallmark of this program, culminating in increases in numbers of awarded grant applications and numbers of manuscripts, oral presentations, and poster presentations at both regional and national levels. Many research advances are emerging from the Partnership. For example, through the Morehouse School of Medicine and University of Alabama Partnership, researchers have identified a possible genetic cause for increased risk for a more advanced form of colorectal cancer in blacks that leads to shorter survival. Understanding the relationship between molecular defects and differences in colorectal cancer incidence, aggressiveness, and clinical outcomes is important in individualizing the treatment and in eliminating racial disparities.

→ For more information, see http://crchd.cancer.gov/research/miccp-overview.html
→ For more information, see http://clincancerres.aacrjournals.org/cgi/content/full/15/7/2406
→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NCI**)

Ethical, Legal, and Social Implications (ELSI) Centers of Excellence: NHGRI's ELSI program has established a network of Centers of Excellence in ELSI Research. Currently, four full Centers and three exploratory Centers are bringing together investigators of diverse expertise to investigate issues related to:

- Intellectual property of genetic information
- Translation of genetic information to health care
- Genetic research that involves human participants
- Use of genetic information and technologies in non-health care settings, such as employment, insurance, education, criminal justice, or civil litigation
- Impact of genomics on the concepts of race, ethnicity, and individual and/or group identity
- Implications of uncovering genomic contributions to human traits and behaviors, such as aging or addictions
- How different individuals, cultures, and religious traditions view the ethical boundaries for the uses of genomics

→ For more information, see http://www.genome.gov/10001618
→ This example also appears in Chapter 3: *Genomics*
→ (E) (**NHGRI**)

Advancing Novel Science in Women's Health Research (ANSWHR): A trans-NIH grants program, ANSWHR, is encouraging innovative, interdisciplinary research that promotes new concepts in women's health research and the study of sex/gender differences. Grants have been funded in areas such as genetic pathways in systemic lupus erythematosus (Lupus), sex differences in stress, sex differences relating to the vulnerability to cocaine addiction, inflammation and insulin sensitivity in obese pregnant women, novel ovarian cancer detection agents, evaluation of diagnostic techniques for cardiovascular events, sex differences in HIV/AIDS antiretroviral treatment, and sex differences and cognitive function. Based on responses to this program, ANSWHR is becoming an important scientific program that is enabling both early-stage investigators and veteran researchers to test nascent scientific concepts.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-07-381.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-07-382.html
→ (E) (**ORWH**, FIC, NCI, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM, OBSSR, ODP/ODS)

Research Enhancement Awards Program (REAP): REAP increases the number of new research studies of women's health and/or the study of sex and gender factors by collaborating with the NIH ICs to identify and co-fund meritorious research grants that have just missed the cutoff for funding. Examples of scientific areas funded through this mechanism included breast reconstruction, estrogen effects on wasting of skeletal muscle, activin target genes in the regulation of ovarian follicle development, and improving contraceptive use and reducing unintended pregnancy rates among young low-income women.

→ For more information, see http://orwh.od.nih.gov/research/recap.html
→ (E) (**ORWH**, NCCAM, NCI, NIAMS, NICHD, NIDCR, NINDS)

Centers of Research Translation (CORT): The NIH CORTs are designed to bring together basic and clinical research to translate basic discoveries into new drugs, treatments, and diagnostics. Each CORT encompasses at least three projects, including one clinical and one basic research study. The centers are:

- The Center for Translating Molecular Signal Pathways to Orthopaedic Trauma Care studies the biological basis of fracture healing and the efficacy of a potential new treatment, teriparatide, an injectable form of human parathyroid hormone that stimulates new bone formation.
- The Center for Lupus Research investigates the role of different cell types in the origin and development of lupus, markers of disease activity and severity, and new targets for treatment.
- The Center for X-Linked Hypophosphatemic Rickets Research focuses on the various molecular contributors to this genetic form of rickets, and works toward developing new treatments.

- The Center for Research Translation in Scleroderma is studying the molecular basis of scleroderma to understand its underlying causes, using functional genomics and gene networks.
- The Center for Genetic Dissection of Systemic Lupus Erythematosus (lupus) studies mouse models of lupus to identify the genetic background of developmental stages of the disease.
- The Center for New Approaches to Assess and Forestall Osteoarthritis in Injured Joints is developing new methods of forestalling post-traumatic osteoarthritis (PTOA).
- The Center for Psoriasis Research Translation uses a Phase I mechanistic, safety, and preliminary efficacy study to test a novel photodynamic therapy for psoriasis.

→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/11_08.asp
→ For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2007/corts.asp
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIAMS**)

Improving Research Efficiency

2009 Institute of Medicine Report, The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors: The recently released IOM report, *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors,* reviews U.S. interest and investment in global health. This report is particularly timely and useful given the major changes in global health that have occurred since the last IOM report, *America's Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests*, was released in 1997. These changes include unprecedented interest and large fiscal commitments to global health by the U.S. government and nongovernmental sectors. The IOM leveraged the contributions of 18 NIH ICs to undertake this update with additional financial support from several key private and public entities. The study makes the case for why U.S. agencies and private sector entities should invest more heavily in global health. The report has five key recommendations that can inform NIH investments in global health in the coming years:

- Scale up existing interventions to achieve significant health gains
- Generate and share knowledge to address health problems endemic to the global poor
- Invest in people, institutions, and capacity-building with global partners
- Increase U.S. financial commitments to global health
- Set the example of engaging in respectful partnerships

The IOM panel was chaired by Dr. Harold Varmus and Ambassador Thomas Pickering. A preliminary report, titled *The U.S. Commitment to Global Health: Recommendations for the New Administration*, was released in December 2008. In May 2009, the final report, titled *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*, was released.

→ For more information, see http://www.iom.edu/Reports/2009/The-US-Commitment-to-Global-Health-Recommendations-for-the-Public-and-Private-Sectors.aspx
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→ This example also appears in Chapter 2: *Cancer*, Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Chronic Diseases and Organ Systems*
→ (O) (**FIC**, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS)

Harmonization of Adverse Event Reporting, Analysis, and Communication: Clinical Research Policy Analysis and Harmonization (CRpac) has led a major effort to improve understanding and compliance with adverse event reporting requirements and to standardize the reporting of adverse event data. An interagency task force, the Federal Adverse Event Task Force (FAET), has been conducting a comprehensive assessment and analysis of existing Federal policies to identify opportunities for greater harmonization in reporting, analyzing, and communicating adverse events in research. The task force, which includes NIH, FDA, OHRP, CDC, AHRQ, VA, and DOD, has developed a core adverse event report that investigators can send to multiple agencies and develop best practices for reporting, analysis, and application of safety information. In addition, FAET has developed a Basal Adverse Event Report (BAER) that provides a single baseline set of information for reporting adverse events and unanticipated problems that is acceptable to multiple Federal agencies. It includes data elements needed for adverse event and unanticipated event reporting across all types of clinical research including behavioral, social science, epidemiologic, and surveillance studies. As a next step, a Web-based portal is under development to provide a seamless online method to submit adverse event reports. The goal is to develop a user-friendly electronic submission system to report an adverse event to NIH, FDA, and other government agencies from investigators, sponsors, physicians, and the public.

→ For more information, see http://oba.od.nih.gov/policy/policy_issues.html#CRP_001
→ (O) (**OSP/OBA**, Common Fund - all ICs participate)

[48] CDC Diabetes Fact Sheet. 2007. For more information, see: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf.
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[54] As required by the NIH Reform Act of 2006, NIH provides an annual report to the U.S. Food and Drug Administration identifying all trials registered in www.clinicaltrials.gov.
[55] Federal Coordinating Council on Comparative Effectiveness Research. Report to the President and the Congress. June 30, 2009. Washington, D.C.: U.S. Department of Health and Human Services. p. 16.
[56] Federal Coordinating Council on Comparative Effectiveness Research. Report to the President and the Congress. June 30, 2009. Washington, D.C.: U.S. Department of Health and Human Services. p. 4.

Disease Registries, Databases, and Biomedical Information Systems

Dr. Mark S. Drapkin, Chief, Infectious Disease Service at Newton-Wellesley Hospital (Newton, MA), was treating a 14-year-old girl diagnosed with the fulminant form of meningococcemia. She was delirious and drifting into shock, and death was a real possibility. Specialist colleagues had no suggestions for new treatment approaches. Although the hospital library was closed for the night, Dr. Drapkin had it opened and did a quick Medline search. The search turned up an article in a British journal that suggested plasmapheresis, a procedure designed to remove excess antibodies from the blood by depleting the body of blood plasma without depleting its blood cells. Using the information from the article, Dr. Drapkin and his colleagues successfully treated the patient. "I would never have found these articles in the limited time frame under which we were working without an electronic search of the literature," said Dr. Drapkin.

Introduction

In a world that is increasingly digital, NIH plays a pivotal role in enabling biomedical research, improving health care and public health, and promoting healthy behavior. By connecting and making the results of research—from scientific data to published literature to patient and consumer health information—readily available, NIH magnifies the positive impact of the Nation's investment in the creation of new knowledge in the pursuit of improved health.

Information has become a primary driver of progress in biomedical research and the health care enterprise. For example, genomic data resulting from sequencing the genes of thousands of patients have become primary resources for identifying the genetic basis of diseases. Data that flow from large-scale clinical studies, advanced diagnostic and imaging equipment, and electronic health records are a key enabler of improvements in clinical practice and individual patient care. Up-to-date information from disease registries has become a critical resource for studying disease incidence and treatment patterns, advancing research, and informing public health interventions. The availability of this and other health information available on the Internet offers consumers a more active role in managing their health and further increases demand for reliable and authoritative health information.

The development, deployment, and utilization of disease registries, databases, and other biomedical information systems are essential to managing large amounts of data for research, clinical care, and public health. Such systems permit the efficient collection, organization, storage, sharing, and accessing of biomedical information. Today's biomedical databases house a wide range of clinical, genomic, and other types of scientific data and information resulting from biomedical research and make it accessible for further research or application. Disease registries collect information on cohorts of patients with specific diseases (e.g., cancer, autoimmune disorders, or Parkinson's disease) or who have received specific treatments (e.g., medical devices). They provide a rich source of information that is used by researchers, clinicians, and policymakers.

Increasingly, disease registries and biomedical databases serve not only as repositories of information, but also as research tools in and of themselves, extending and in some cases augmenting the laboratory. Discoveries can be made by examining the information contained in them. For example, scientists can use molecular databases to study the profiles of individual tumors and conceptualize small-molecule anticancer agents to target them. They can analyze large-scale databases linking genotype and phenotype information from thousands of individuals to identify genes associated with particular observable traits (e.g., obesity) or diseases (e.g., diabetes, cancer). In these ways, biomedical information systems are changing the nature of research itself, and promise to change the nature of clinical care and public health.

The utility of disease registries, databases, and biomedical information systems rests on many factors, including data quality, user accessibility, ease of search capability, availability of useful tools for analysis, and their ability to interoperate

with other systems. New data must be added on a regular basis, while existing data are maintained or updated to reflect new findings. Improved search tools are needed to comb through the massive datasets and retrieve relevant results. Standard vocabularies are needed to efficiently organize information, facilitate effective linking and sharing of information, and ensure accurate retrieval, and they, too, must be updated to accommodate new concepts and relationships. New analytical tools are needed to explore increasingly complex questions, such as how the expression patterns of multiple genes are associated with a particular trait or response. Such tools are most effective when information systems are interoperable and can communicate, exchange data, and make use of similar software applications. Given the critical importance of data to biomedical research and health care, policies and procedures are needed to encourage researchers to submit relevant data and to provide other researchers, clinicians, and the general public with suitable access to the data, while simultaneously protecting the confidentiality of personally identifiable information. Preserving, protecting, and ensuring the validity and security of information stored in biomedical databases remains of paramount importance.

Because of the growing importance of information and its management in biomedical science, clinical care, and public health, virtually every NIH IC is engaged in the development, deployment, and use of biomedical information systems that support its mission.

Because of the growing importance of information and its management in biomedical science, clinical care, and public health, virtually every NIH IC is engaged in the development, deployment, and use of biomedical information systems that support its mission. NIH databases and information systems have become indispensable national and international resources for biomedical research and public health. Several trans-NIH activities feature the development of significant biomedical information resources, including the tools, infrastructure, and associated research needed to make databases and registries more valuable. Many of the challenge grants supported with funds from the American Recovery and Reinvestment Act of 2009 (ARRA) relate to data systems and tools, focusing on a wide variety of informatics topics such as new computational and statistical methods for the analysis of large datasets from genome-wide association studies (GWAS) and the use of next-generation sequencing technologies, intelligent search tools for answering clinical questions, and new information technology and resources for disease prevention and personalized medicine.

This section of the Biennial Report describes NIH efforts to develop and deploy disease registries, databases, and biomedical information systems to advance biomedical science, health, and health care. It focuses on:

- Scientific Databases. These databases archive and provide access to authoritative scientific literature, essential research data (including disease-specific data), and clinical research information.
- Genomic Information Systems. Major systems include GenBank for genomic sequence data and dbGaP (database of Genotype and Phenotype) for GWAS data.
- Disease Registries and Surveillance Systems. NIH works with other Federal and private entities to integrate disease registries for national and local use. For example, the Surveillance, Epidemiology, and End Results (SEER) program has been the foundation for innumerable studies, including recent research into links between hormone therapy and breast cancer.

Emphasis is placed on intramural and extramural activities in which development and maintenance of such information resources is a primary objective, rather than a means of achieving another objective. The described disease registries, databases, and biomedical information systems are intended for widespread use by researchers, clinicians, public health officials, or the general public, and some are associated with policies that require or encourage the submission of particular data or information.

This section of the Biennial Report also describes NIH efforts to make these and other data systems more useful to researchers, clinicians, and the public. Of particular interest are activities related to the following:

- Standardized Vocabularies and Data Protocols. NIH leads the government's efforts to develop standardized vocabularies and terminology to support interoperability among biomedical information systems in research and clinical settings.
- Large-Scale Informatics Infastructure. NIH funds the development of large-scale systems and tools that allow communities of researchers to collect, share, and analyze data needed for research, clinical care (including electronic health records), and public health.
- Biomedical Informatics Research and Training. NIH is the largest Federal funder of biomedical informatics research, which aims to advance the applications of computing to biomedicine for both research and clinical care. Grant programs support research and training in medical informatics and medical librarianship.

Recent developments in policies and procedures to encourage the submission of data to NIH's disease registries, databases, and biomedical information systems also are reviewed.

Catalog of Disease Registry, Database, and Biomedical Information System Activities

In response to the mandate under SEC. 403 (a)(4)(C)(ii) of the Public Health Service Act to provide catalogs of disease registries and other data systems, included here is a live link to an inventory of NIH intramural and extramural activities ongoing in FYs 2008 and 2009 to develop or maintain databases, disease registries, and other information resources for the benefit of the larger research community. Based on a future assessment of the information collected in the inventory, NIH potentially may develop capacity to integrate this catalog as a new category within the NIH RCDC process.

Summary of NIH Activities

NIH Scientific Databases: Enhancing Access to Research Information

Keeping pace with the expanding volume of biomedical knowledge is a continuing challenge for scientists, clinicians, policymakers, and the public; thus, NIH devotes considerable attention and resources to developing, expanding, and maintaining tools and resources for information management. Biomedical databases store and provide access to a wide range of information, from the results of scientific or clinical research studies, to genomic information, to standard reference materials (such as genome sequences or anatomical images), to published journal articles and citations to the medical literature. They are widely used by biomedical researchers, as well as by a growing number of clinicians, public health officials, and consumers. NIH often undertakes special initiatives to make these resources more accessible to a broader, more diverse set of users.

Among the most widely used of NIH's databases are those that collect and provide access to **scientific literature**. These comprehensive resources are extensively used by scientists, health care providers, and consumers who seek trusted, peer-reviewed information on biomedical and health topics of interest. NIH houses the leading source of authoritative biomedical literature for professional and lay audiences. NIH's exhaustive PubMed/MEDLINE database, for example, indexes citations to articles in more than 5,300 peer-reviewed scientific journals. It contains references to more than 16 million journal articles in the life sciences, and 1.4 million new citations were added to the system during the 2-year period from FY 2008 to FY 2009. During the FY 2008-2009 biennial period, PubMed logged more than 1.5 billion Web-based searches.

The PubMed/MEDLINE database indexes citations to articles in more than 5,300 peer-reviewed scientific journals and contains references to more than 16 million journal articles in the life sciences. Almost 1.4 million new citations were added to the system during the 2-year period from FY 2008 to FY 2009.

In addition, NIH continues to expand PubMed Central (PMC), its digital archive of full-text scientific journal articles. PMC was established to provide online access to a growing number of scientific journal articles deposited by publishers and NIH-funded researchers. Between February 2007 and September 2009, the number of articles available in PMC

doubled to 1.9 million and usage rose by more than 60 percent to 360,000 users per day. Some of this increase is attributable to an expanding scope of users—not just biomedical researchers, but also clinicians, other practitioners, and consumers—which highlights the importance of this type of resource.

PMC serves as the repository for manuscripts submitted in accordance with the NIH Public Access Policy, which became mandatory in 2008. The policy ensures that the public and the scientific community have access to the published results of NIH-funded research by requiring NIH-funded scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to PMC. Manuscripts are to be submitted upon acceptance for publication and made accessible to the public no later than 12 months after publication. PMC software also is used by funding agencies in other countries to establish repositories for their funded research. The Wellcome Trust and other major research funders in the United Kingdom established a site that has been operational since 2008, and in 2009, NIH partnered with the Canadian Institutes of Health Research and the National Research Council's Canada Institute for Scientific and Technical Information to establish PMC Canada.

To further facilitate rapid access to emerging scientific findings, NIH announced in August 2009 the introduction of Rapid Research Notes (RRN), a resource to archive research results made available through online venues for rapid scientific communication. The RRN archive allows users to access research that is provided through participating publisher programs for immediate communication. Creation of such an archive had been discussed for many years, but the outbreak of 2009 H1N1 influenza in the spring of 2009 provided increased impetus for the project. The first collection to be archived in RRN will be an open-access, online resource for immediate communication and discussion of new scientific data, analyses, and ideas in the area of influenza. NIH expects the RRN archive to expand over time to include additional collections in other high-interest biomedical fields.

To further facilitate rapid access to emerging scientific findings, NIH announced in August 2009 the introduction of Rapid Research Notes, a resource to archive research results made available through online venues for rapid scientific communication.

NIH actively endeavors to make its information resources more accessible to varied types of users, as illustrated by its work on MedlinePlus, NIH's comprehensive health information source for consumers and health professionals. Another information source that is directed at a wide variety of users is Genetics Home Reference, NIH's website for consumer-friendly health information on genetic conditions. This information resource bridges consumer health information and scientific bioinformatics data and links to many existing resources at NIH and at other reliable sites.

NIH also puts effort into developing and maintaining information systems that collect data stemming from **biomedical research**, organize it, and make it accessible for subsequent research. NIH's PubChem database, for example, houses data flowing from the high-throughput bioassay centers that were established with NIH funding under the Molecular Libraries Initiative of the NIH Roadmap. It provides information about the biological activity of small molecules, organized as three linked databases along with a chemical structure similarity search tool. The number of unique compounds represented in PubChem more than doubled during FYs 2008-2009 from approximately 10 million to more than 25 million, while the number of bioassays rose from 600 to 1,700. As a result, PubChem provides bioactivity results from more than 50 million tests of small molecules. The number of users per day also increased from approximately 30,000 to 50,000. PubChem is integrated with NIH's Entrez suite of biomedical information resources, enabling users to retrieve related data from multiple databases and navigate among them with relative ease.

NIH is one of three Federal agencies to fund the Protein Data Bank (PDB), an archive of information about experimentally determined structures of proteins, nucleic acids, and complex assemblies. Information on more than 13,000 structures was added to the PDB in FYs 2008-2009, bringing its total content to more than 60,000 molecules. PDB allows users to search for molecules based on their sequence, structure, or function and provides tools to visualize and analyze downloaded structures.

TOXNET is a cluster of 13 large databases covering toxicology, hazardous chemicals, environmental health, and related topics. TOXNET includes literature-based and research databases. It has been used by toxicologists for decades, assisting them in locating toxicology data, literature references, and toxic release information on particular chemicals, as well as in identifying chemicals that cause specific health effects. Peer-reviewed studies from the National Toxicology Program are used by State, local, and Federal health officials to assess the toxicologic potential of environmental compounds to cause adverse health effects such as cancer. To make the Hazardous Substances Data Bank component of TOXNET more useful to first responders at the scene of a disaster, NIH developed WISER, the Wireless Information System for Emergency Responders, which enables wireless access to a selection of the most relevant data for emergency responders. WISER can be installed on personal digital assistants, providing emergency personnel with access to critical information for identifying and safely cleaning up spilled chemicals, understanding their health effects, treating exposed victims, and assessing environmental impact.

To make the Hazardous Substances Data Bank component of TOXNET more useful to first responders at the scene of a disaster, NIH developed WISER, the Wireless Information System for Emergency Responders, which enables wireless access to a selection of the most relevant data for emergency responders.

NIH launched the National Database for Autism Research (NDAR) in FY 2009 as a repository for human subjects data stemming from autism research. NDAR hosts genetic, imaging, and phenotypic research data related to autism and makes it accessible to qualified researchers. The system provides researchers with standards to enable them to analyze and compare data from multiple research sites and different bioinformatics systems. It also offers bioinformatics tools for depositing, validating, and searching for information. Its collaboration mechanisms allow for sharing quality research data within the autism research community. NIH-funded researchers are strongly encouraged to share their data with NDAR to enable secondary use and analysis.

Another group of NIH-supported databases organize and provide access to **clinical research information**. NIH's ClinicalTrials.gov database was significantly enhanced during FYs 2008 and 2009 to respond to the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85), which expands the types of clinical trials that must be registered in ClinicalTrials.gov, increases the amount of information that must be submitted for each trial, and requires the submission of summary results data, including adverse events. During FYs 2008 and 2009, more than 34,000 trials were registered with ClinicalTrials.gov, raising the total number of registered trials in the system to 80,000. During that same time period, summary results of more than 830 trials were submitted to the system and made available to the research community and the general public.

In addition, the NIH Biomedical Translational Research Information System (BTRIS), which was initiated in 2008, was made available to the intramural NIH community in 2009. BTRIS is a powerful new tool for NIH investigators to access clinical research data, develop streamlined mechanisms for protocol reporting and data analysis, and reuse data for hypothesis generation and collaboration. New functionality will continue to be added to the system.

ProtoType is an assisted protocol authoring tool that provides a systematic framework where research protocols can be developed and maintained throughout their life cycle. ProtoType includes fully customized documents tailored toward individual Institutional Review Boards, allowing investigators to focus on the substance of their protocols, rather than the formatting.

Genomic Information Systems: Understanding the Genetic Basis of Disease

NIH also has made great strides in developing information resources to support genetics research. NIH has long supported genetics research through widely used resources such as GenBank, the NIH genetic sequence database. In FY 2009, NIH launched the Sequence Read Archive (SRA) to accommodate the massive quantities of data coming from sequencing projects that are using new high-throughput technologies. SRA is proving to be one of the fastest growing biological

databases in history, with more than 10 terabytes of sequence data under management at the end of FY 2009 and a growth rate of about 1 terabyte per month. NIH's Influenza Virus Resource database, comprising information obtained from the NIH Influenza Genome Sequencing Project and GenBank, contains more than 90,000 influenza virus sequences, including the sequences of more than 2,000 whole influenza genomes. In spring 2009, with the rapid emergence of the 2009 H1N1 pandemic, the database received more than 2,200 influenza sequences from the Centers for Disease Control and Prevention and laboratories from 35 countries. This resource enables scientists to compare influenza virus strains so that emergent variants can be identified more rapidly and vaccines developed accordingly. As the library of viral sequences grows, it will be an increasingly important reference to help further understand how avian viruses spread to humans, and how influenza activity spreads throughout the world.

Considerable effort has been aimed at supporting the analysis of data from GWAS, which explore the connection between specific genes (genotype information) and observable diseases or conditions (phenotype information, such as diabetes, high blood pressure, or obesity). NIH's dbGaP (database of Genotype and Phenotype) houses data from a number of GWAS, including those funded by NIH. By the end of 2009, dbGaP included results from more than 40 GWAS, including genetic analyses related to such diseases as Parkinson's disease, amyotrophic lateral sclerosis, diabetes, alcoholism, lung cancer, and Alzheimer's disease. NIH's GWAS policy, which went into effect in January 2008, encourages NIH grantees to submit their GWAS data to dbGaP and establishes procedures for making it available to other researchers to speed up disease gene discovery while at the same time protecting the privacy of research subjects in genomics studies.

By the end of 2009, dbGaP (database of Genotype and Phenotype) included results from more than 40 genome-wide association studies, including genetic analyses related to such diseases as Parkinson's disease, amyotrophic lateral sclerosis, diabetes, alcoholism, lung cancer, and Alzheimer's disease.

In addition, several NIH ICs have established genetics repositories to accelerate research and multidisciplinary collaborations in specific disease areas. Programs such as the NEI eyeGENE, NIMH Genetics Repository, the NINDS Human Genetics Repository, the NIEHS Chemical Effects in Biological Systems (CEBS) Knowledge Base, and the NIA Genetics of Alzheimer's Disease Data Storage Site give researchers access to vast storehouses of genetic and genomic data, DNA samples, and clinical data, along with informatics tools designed to facilitate their analyses. The wide availability of information linking genotype to phenotype should help researchers better understand gene-based diseases and speed development of effective therapies.

Other NIH-supported genetic databases contain information on model organisms, which are widely used by researchers to understand disease processes and develop new therapeutic strategies and tools that can be transferred to humans. The NIH-funded Rat Genome Database, for example, combines information on the genome, genes, and disease traits of different strains of rats with related information on the mouse and human genomes. WormBase is an international consortium of biologists and computer scientists dedicated to providing the research community with accurate, current, accessible information concerning the genetics, genomics, and biology of *C. elegans* and related organisms. The Universal Protein Resource (UniProt) Knowledgebase offers the scientific community free access to a comprehensive source of information on protein sequences and related functional information.

Disease Registries and Surveillance Systems: Tracking and Monitoring Disease

Disease registries collect information about the occurrence of specific diseases, such as cancer and Parkinson's disease, the kinds of treatment that patients receive, and other information that might be relevant to researchers or public health officials. Increasingly, disease registries also include genomic data from registered patients. Registry information can therefore help identify causal factors of disease, assess the effectiveness of various interventions, and identify questions of concern to researchers, clinical professionals, and policymakers.

NIH-supported disease registries have paid many dividends over the years. Recently, for example, with the participation of patients from the Alopecia Areata Registry, NIH-supported scientists discovered four chromosomal locations that appear to be associated with susceptibility to this common autoimmune disease, which is characterized by patchy hair loss. Understanding the mechanisms of the genes found at these locations could lead to the development of an effective treatment for the disease, which is presently untreatable.

Disease registries have been employed for research on other autoimmune disorders, including Sjogren's Syndrome, one of the most prevalent. A significant roadblock for moving discoveries ahead in the field of Sjogren's Syndrome is a lack of data and biospecimens available for research. Recognizing the problem, NIH spearheaded an effort to establish patient registries at two extramural institutions, as well as through its own intramural program. These groups work together to generate and share genome-wide genotyping data and clinical information from the cohorts enrolled through these efforts with the general research community. Similarly, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) aims to establish centers in multiple regions of the world for the collection and harmonization of data that can be used by an international research consortium to address unique and evolving research questions in HIV/AIDS that are currently unanswerable by single cohorts. High-quality data are being collected by researchers throughout the world. This initiative provides a means to establish and implement methodology to effectively pool the collected data—thus providing a cost-effective means of generating large datasets to address high-priority research questions.

The inclusion of genomic information in disease registries makes them valuable resources for investigating the contribution of genes and genetic variation to diseases of interest. To spur such research, NIH collaborated with the University of North Carolina's General Clinical Research Center to launch a large volunteer DNA banking project named the Environmental Polymorphisms Registry (EPR), which will collect DNA samples from up to 20,000 individuals in the greater North Carolina Triangle Region. These samples will be available to scientists to look for genes that may be linked to common diseases such as diabetes, heart disease, cancer, asthma, and many others. In addition, NIH supports the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). The goal of GenTAC is to establish a registry of patients with genetic conditions that may be related to thoracic aortic aneurysms—a disorder that weakens the main artery from the heart—and to collect medical data and biologic samples. The samples and data are made available to qualified investigators to enable research on effective medical practices and to advance the clinical management of genetic thoracic aortic aneurysms, and other cardiovascular complications. NIH supports several other registries associated with specific diseases, including lupus, muscular dystrophy, and rheumatoid arthritis.

The International Epidemiologic Databases to Evaluate AIDS aims to establish centers in multiple regions of the world for the collection and harmonization of data that can be used by an international research consortium to address unique and evolving research questions in HIV/AIDS that are currently unanswerable by single cohorts.

Registries also serve as an effective mechanism to gather data on the incidence, prevalence, and natural history of diseases. The NIH-supported California Parkinson's Disease Registry, for example, enables researchers to identify the possible environmental and genetic origins of this progressive neurological disorder suffered by an estimated 1.5 million Americans. Data in the registry can help to determine whether race, ethnicity, gender, age, environmental factors, or place of residence influence the likelihood of getting the disease, and can help track incidence and demographic trends.

Registries also provide a valuable source of information for tracking the effectiveness of particular treatments or interventions. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), for example, is a national registry for patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure. The registry is supported jointly by NIH, the Food and Drug Administration, and the Centers for Medicare and Medicaid Services. Use of standardized terminologies helps ensure that the data collected will facilitate improved patient

evaluation and management while aiding in better device development. INTERMACS also is expected to facilitate appropriate regulation and reimbursement of the implantation of mechanical circulatory support devices.

Registries also are integral elements of more comprehensive NIH programs designed to monitor and analyze disease trends in the United States. For example, the SEER program has a 35-year track record of identifying emerging trends, geographic variation, ethnic disparities, and other patterns that have provided new directions for epidemiologic research into the cause, progression, and control of cancer. SEER collects and publishes cancer incidence and survival data from cancer registries covering approximately 26 percent of the American population. De-identified data is made available for research, and an interactive query system is available on its website. SEER data provided critical insight into the relationship between hormone therapy and breast cancer incident rates. SEER data recently have been enhanced by linking persons in SEER to Medicare enrollment and utilization data. The SEER-Medicare data are longitudinal and can be used to assess health care received prior to a cancer diagnosis, at the time of diagnosis, and after initial treatment until death. There have been more than 400 peer-reviewed publications resulting from SEER-Medicare data, adding to the thousands of publications based on SEER.

Surveillance and monitoring programs also are crucial sources of information and analysis for policymakers, legislators, public health officials, clinicians, and the public. SEER participates in Cancer Control P.L.A.N.E.T., a Web portal that provides links to comprehensive cancer control resources and data for public health professionals. NIH supports several epidemiologic programs designed to gather ongoing data and monitor emerging drug abuse trends in adolescents and other populations, helping to guide national and global prevention efforts, drug control, and public health policy. Among the projects are the Monitoring the Future (MTF) Survey, which has been tracking trends in substance use, attitudes, and beliefs among adolescents and young adults in the United States since 1975, and the Community Epidemiology Work Group (CEWG), which provides ongoing community-level surveillance of drug abuse through analysis of quantitative and qualitative research data. CEWG findings reported in 2008 and 2009 show decreases in methamphetamine indicators (e.g., treatment admissions), suggesting that the problems that had escalated in the first half of the decade may have stabilized or declined.

NIH supports several epidemiologic programs designed to gather ongoing data and monitor emerging drug abuse trends in adolescents and other populations, helping to guide national and global prevention efforts, drug control, and public health policy.

NIH also supports the Alcohol Policy Information System (APIS), an online database that provides detailed information on a wide variety of alcohol-related policies in the United States at both State and Federal levels. Designed primarily as a tool to encourage and facilitate research on the effects and effectiveness of alcohol-related public policies in the United States, APIS simplifies the process of ascertaining the state of the law for studies on the effects and effectiveness of alcohol-related policies.

Standardized Vocabularies, Data Protocols, and Tools

NIH continues to invest in tools that can increase the utility of its scientific databases and medical information sources. A key component of such efforts relates to the development and maintenance of standards and vocabularies for use in information systems used for research and clinical care, including electronic health records. Medical terminology can be difficult to remember and can vary from one laboratory or clinical facility to another. Often there are many names for a single concept (e.g., cancer of the colon, colonic neoplasm, colon cancer). Standard vocabularies and ontologies (models of the relationships between concepts) improve information search, retrieval, and exchange by endowing systems with the ability to automatically perceive and retrieve information about related terms. As expansion of scientific frontiers produces new concepts, terms, and relationships, standard vocabularies must be regularly revised so that articles and other data can be properly indexed and search engines can find relevant and related terms.

NIH continues to update the Unified Medical Language System (UMLS), which is used heavily in advanced biomedical research and data mining worldwide. The UMLS Metathesaurus, with more than 7.7 million concept names from more than 100 vocabularies, is a distribution mechanism for standard code sets and vocabularies used in health data systems. Many institutions apply UMLS resources in a wide variety of applications including information retrieval, natural language processing, creation of patient and research data, and the development of enterprise-wide vocabulary services for electronic health records.

NIH is pursuing research and development on robust and scalable approaches to synthesizing, representing, updating, and deploying electronic knowledge and decision algorithms for use in conjunction with electronic health records.

The broad deployment and use of advanced electronic health records will provide expanded opportunities for access to biomedical knowledge and advanced decision support for the public, their health care providers, and the public health workforce. To turn this potential into effective reality, NIH is pursuing research and development on robust and scalable approaches to synthesizing, representing, updating, and deploying electronic knowledge and decision algorithms for use in conjunction with electronic health records. NLM serves as the central coordinating body for clinical terminology standards across the HHS and works closely with the Office of the National Coordinator for Health Information Technology (ONC) to support nationwide implementation of an interoperable health information technology infrastructure. NIH develops and licenses key clinical terminologies that are designated as standards for health information exchange in the United States. It produces RxNorm, a standard clinical drug vocabulary, supports the Logical Observation Identifiers Names and Codes (LOINC) nomenclature for laboratory tests and patient observations, and collaborates with the International Health Terminology Standards Development Organisation to promote international adoption of the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT). In FY 2009, NIH released the first version of the CORE Problem List Subset of SNOMED CT, designed to facilitate coding of problem list data in electronic health records by mapping frequently used terms from seven large-scale health care institutions to corresponding SNOMED CT concepts. (The problem list is often the first part of the clinical narrative in an electronic health record that is codified with some controlled vocabulary.) The Newborn Screening Codes and Terminology Guide, a Web portal to support more effective use of newborn screening laboratory test information, was created in FY 2009 in collaboration with the ONC, the Health Resources and Services Administration, and newborn screening organizations.

Common terminologies are a key enabler of related research and development to exploit the inherent relationships among information in disparate databases and support the interlinking of data systems. PubChem's chemical structure and bioassay records, for example, are interlinked with the biomedical literature in PubMed and with three-dimensional protein structure records. This integration provides many routes by which biomedical researchers may discover the candidate probes developed by the Molecular Libraries Initiative. A researcher examining a protein sequence record, for example, may see that a particular protein has been screened, view the active compounds, and examine structure-activity relationships using PubChem analysis tools. Another NIH resource, the Daily Med, is an official distribution mechanism for FDA-approved packaging information (drug label inserts) that links to other sources of drug information, including MedlinePlus, ClinicalTrials.gov, and PubMed. More than 60,000 people subscribe to its RSS data feeds.

NIH's Discovery Initiative, launched in FY 2006-2007 and continuing into FY 2008-2009 aims to take database linking to the next level. The Discovery Initiative will improve the presentation of results from search queries conducted across a range of NIH databases so that users, who often do not go beyond retrieving the basic results of a search query, are more likely to be drawn to related information that could lead to serendipitous discoveries, even if that information resides in another NIH database. NIH's Collective Intelligence Initiative aims to facilitate data re-use and knowledge discovery by using controlled vocabularies and ontologies to pull together and analyze related information from databases across the ICs.

Large-Scale Informatics Infrastructure

NIH also has embarked on a number of large-scale initiatives to develop and deploy infrastructure and tools for storing, sharing, integrating, and analyzing the large volumes of data routinely generated in research laboratories and in clinical settings. These initiatives tend to produce not only storehouses for data generated by research, but also larger scale networks for sharing data, linking researchers, and conducting further research. NIH supports a number of clinical research networks, for example, infrastructure that allows standardized data reporting and sharing of information across clinical studies. (Also see the section on *Clinical and Translational Research* in Chapter 3.)

In the area of cancer research, NIH has established the Cancer Biomedical Informatics Grid® (caBIG®), a collaborative information network for all of NCI's advanced technology and program initiatives that aims to enable collaborative research and personalized, evidence-based care. The network connects scientists, practitioners, and patients, enabling the collection, analysis, and sharing of data and knowledge along the entire research pathway from bench to bedside. Specific biomedical research tools under development by caBIG® include clinical trial management systems, tissue repositories and pathology tools, imaging tools, and a rich collection of integrative cancer research applications. Ongoing collaborations with research and bioinformation organizations in China, India, and the United Kingdom are driving international adoption of caBIG® resources. The caBIG® infrastructure also supports a new health care ecosystem, BIG Health, launched in 2008 in collaboration with various stakeholders in biomedicine (e.g., government, academia, industry, nonprofits, and consumers) in a novel organizational framework to demonstrate the feasibility and benefits of personalized medicine. BIG Health will provide the foundation for a new approach in which clinical care, clinical research, and scientific discovery are linked.

Other efforts aim to provide the informatics infrastructure to advance basic research and clinical studies across the spectrum of biomedical sciences. NIH's Biomedical Informatics Research Network (BIRN) is a virtual community of shared informatics resources. BIRN's grid computing technology makes digital research data freely available for sharing and exchange among communities of researchers; its data integration tools allow searching across distributed databases; and it provides tools for data analysis, management, and collaborative research. (Also see the section on *Technology Development* in Chapter 3.) The CardioVascular Research Grid (CVRG) provides infrastructure for sharing cardiovascular data and data analysis tools. The CVRG builds on and extends tools developed in the caBIG® and BIRN projects to support national and international collaborations in cardiovascular science.

A Disaster Information Management Research Center was established in FY 2008 to facilitate access to disaster information, promote more effective use of libraries and disaster information specialists in disaster management efforts, and ensure uninterrupted access to critical health information resources when disasters occur.

The Neuroscience Information Framework (NIF), part of NIH's Neuroscience Blueprint, aims to advance neuroscience research by enabling discovery and access to research data and tools worldwide through an open source, networked environment. By the end of FY 2009, more than 2,300 Web-accessible information resources were listed in the NIF registry. NIF also supports the NeuroLex project, which aims to define neurological terms and their relationships to simplify information retrieval and sharing. NeuroLex consisted of approximately 17,000 neuroscience concepts at the end of FY 2009. A related effort, the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC), facilitates finding and comparing structural and functional neuroimaging tools and resources. Collecting and pointing to standardized information about tools, this site helps researchers find the right structural or functional neuroimaging tool or resource and determine whether it can contribute to a given research endeavor. More than half the tools available through the Clearinghouse previously were unavailable for sharing. Since its release at the beginning of FY 2008, more than 50,000 software files have been downloaded from its award-winning website.

The Bioinformatics and Computational Biology initiatives of the NIH Roadmap continue to make progress toward creation of a national biomedical data and information management system. Through the system, biologists, chemists,

physicists, computer scientists, and physicians anywhere in the country will be able to use a common set of software tools to analyze, integrate, model, simulate, and share data. The National Centers for Biomedical Computing are a central focus of this effort, providing funding for seven centers that cover systems biology, image processing, biophysical modeling, biomedical ontologies, information integration, and tools for gene-phenotype and disease analysis. The Centers collaborate with other NIH-funded institutions on topics ranging from biomechanics to standards development for data mining, and cross-Center working groups pursue activities of common interest, such as Biositemaps, which assist users in locating, querying, composing or combining, and mining biomedical information from databases that are distributed across the Centers.

NIH also develops advanced information infrastructure to assist emergency responders when disaster strikes. A Disaster Information Management Research Center was established in FY 2008 with the aim to facilitate access to disaster information, promote more effective use of libraries and disaster information specialists in disaster management efforts, and ensure uninterrupted access to critical health information resources when disasters occur. A disaster information website provides access to a broad range of emergency preparedness and response information. The Center also collaborates with the Navy National Medical Center, Suburban Hospital, Johns Hopkins Medicine, and the NIH Clinical Center through the Bethesda Hospital Emergency Preparedness Partnership. The Partnership provides backup communication systems and develops tools for patient tracking, information sharing and access, and responder training, serving as a model for hospitals across the Nation.

Biomedical Informatics Research and Training

Ensuring continued advances in biomedical informatics resources requires active support of fundamental research that seeds the further development of new tools, resources, and approaches. It also is critical to generate a continuous supply of skilled biomedical informatics researchers, information specialists (such as medical librarians), and life sciences researchers trained in bioinformatics. NIH continues to expand its efforts in bioinformatics research and training in response to the growing importance of informatics in the biomedical and life sciences.

NIH supports research in new technologies to address issues such as: interoperability of data systems, compatibility of computer software across medical institutions, security of data during transmission, compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), availability of affordable data systems for patient care providers, and integration of medical decision support information in medical data systems. Several ICs fund informatics research projects within their areas of specialization. NLM remains the primary Federal sponsor of biomedical informatics research, and its extramural grants program supports research on the characterization, management, and efficient use of data, information, and knowledge in health care and basic biomedical sciences. Grants funded in FY 2008-2009 explored informatics challenges related to clinical care, biomedical research, genomics, and public health. NLM's most recent long-range plan, *Charting a Course for the 21st Century,* identifies a number of emerging informatics challenges that will demand continued research and development.

Funds from the American Reinvestment and Recovery Act will allow NIH to support an additional 56 2-year slots at 10 of its training programs for 2009 and 2010.

NIH also is the principal source of support for research training in biomedical informatics, providing research training grants to 18 institutions that enrolled 270 trainees in FY 2009. ARRA funds will allow NIH to support an additional 56 2-year slots at 10 of its training programs for 2009 and 2010. NIH also implemented a Diversity Short-Term Trainee Program in FY 2008 that supported 18 trainees in 7 training programs and sponsors an Informatics Training for Global Health Program, which supports informatics research training in low- and middle-income country institutions in partnership with U.S. institutions and investigators. Training is integrated with ongoing research at the foreign institutions to develop informatics capacity and support research. Training must address the health and informatics needs of the collaborating countries. (Also see the section on *Research Training and Career Development* in Chapter 3.)

Conclusion

The results of NIH's commitment to disease registries, databases, and biomedical information systems are apparent in the following highlights describing some of the important accomplishments and ongoing initiatives.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

NIH Scientific Databases: Enhancing Access to Research Information

PubMed®/MEDLINE®: NIH continued to expand PubMed/MEDLINE as a tool for biomedical research, clinical medicine, and consumer health. Nearly 1.4 million articles from the biomedical journal literature were added to PubMed/MEDLINE in FYs 2008-2009. The Indexing 2015 initiative continues to pursue increases in the speed and efficiency of indexing through natural language processing and other automated techniques, and in FYs 2008-2009, the GPRA goal of reducing the time to catalog new journals added to NLM's collection was achieved. Drawing on results of the NCBI Discovery Initiative, enhancements were made to PubMed search capabilities to expand the number and highlight the visibility of links to related information across multiple databases.

→ For more information, see http://pubmed.gov
→ (I) (NLM) (GPRA)

PubMed Central (PMC): NIH made significant enhancements to PMC, an online repository of full-text biomedical journal articles. Since February 2007, PMC has doubled the number of articles to 1.9 million in September 2009. Usage also has risen by 60 percent to more than 360,000 users per day. A part of the growth has stemmed from the NIH Public Access policy changing from a voluntary to a mandatory program in April 2008. Under the Public Access policy, all NIH-funded research articles must be deposited in PMC. The NIH Manuscript Submission system streamlines the process for NIH-funded authors submitting their manuscripts to PMC, and more than 5,000 manuscripts a month are received, compared to less than 1,000 under the previous voluntary Public Access policy in 2007. Through PMC agreements with publishers, a growing number of journals, now more than 700, offer full text of their contents to PMC either immediately upon publication or within 12 months. To foster international cooperation on preservation and access to biomedical literature, NIH made PMC software available to archiving organizations outside the United States and worked with the Wellcome Trust and other major United Kingdom (UK) research funders to establish a collaborating PMC site in the UK, which has been operational since 2008. In 2009, NIH partnered with the Canadian Institutes of Health Research and the National Research Council's Canada Institute for Scientific and Technical Information to establish PMC Canada.

→ For more information, see http://www.pubmedcentral.nih.gov
→ For more information, see http://ukpmc.ac.uk
→ (I) (**NLM**)

PubChem: PubChem is an open repository for data on the properties of small molecules, including bioactivity test results. It began in 2004 as part of NIH's Molecular Libraries Program, which aims to discover new chemical probes through high-throughput biological screening. As of FY 2009, there were more than 25 million unique structures and 1,700 bioassays. These assays contain information on the biological activities of 700,000 compounds, yielding more than 50 million bioactivity results, and have been contributed by 34 academic, government, and commercial organizations. Through the PubChem website, more than 50,000 scientists a day rapidly search chemical structures, retrieve and compare screening results, explore structure-activity relationships, and identify potential molecular targets.

→ Wang Y, et al. *Nucleic Acids Res* 2009;37(Web Server issue):W623-33. PMID: 19498078. PMCID: PMC2703903.
→ For more information, see http://pubchem.ncbi.nlm.nih.gov/
→ (I) (**NLM**)

TOXicology Data NETwork (TOXNET): TOXNET is a cluster of 13 databases covering toxicology, hazardous chemicals, environmental health, and related topics. It is a primary reference for toxicologists, poison control centers, public health administrators, physicians, and other environmental health professionals, and includes databases such as Hazardous Substances Data Bank, TOXLINE, GENE-TOX, and the Toxic Release Inventory. In FY 2008, the Carcinogenic Potency Database at the University of California, Berkeley, which reports analyses of animal cancer tests and is in support of cancer risk assessments, was added to the databases searchable through the TOXNET search engine. TOXNET is highly used, with nearly 600,000 users in FYs 2008 and 2009. Enhancements based on user feedback were made in FY 2008.

→ (I) (**NLM**)

National Database for Autism Research: The National Database for Autism Research (NDAR) is a collaborative biomedical informatics system created by NIH to provide a national resource to support and accelerate research in autism spectrum disorder (ASD). NDAR hosts human genetic, imaging, and phenotypic research data relevant to ASD, making these data available to qualified researchers. NDAR also has the capability to allow investigators to use NDAR for data sharing among select collaborators in ongoing studies. Through its Data Dictionary, NDAR will foster the development of a shared, common understanding of the complex data landscape that characterizes ASD research. Finally, its architecture facilitates linkage of NDAR with other significant data resources, regardless of their location or ownership and in ways that respect the policies and implementations of those other data resources.

→ For more information, see http://ndar.nih.gov/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E/I) (**NIMH**, CIT, NICHD, NIDCD, NIEHS, NINDS)

National NeuroAIDS Tissue Consortium: The National NeuroAIDS Tissue Consortium (NNTC) is a repository of brain tissue and fluids from highly characterized HIV-positive individuals. Established as a resource for the research community, the NNTC includes information from more than 2,280 participants in its clinical evaluation/tissue donation program, including nearly 750 brains, thousands of plasma and cerebrospinal fluid samples, and additional organs and nerves of interest.

→ For more information, see http://www.hivbrainbanks.org/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E/I) (**NIMH**, NINDS)

ClinicalTrials.gov: ClinicalTrials.gov was significantly modified during FY 2008-2009 to respond to new clinical trial registration and results reporting requirements established by the FDA Amendments Act of 2007 (PL 110-85). The existing registry was expanded to accommodate the submission of more information about a larger number of trials, including those trials of FDA-regulated drugs, biological products and devices that now are required to register. In addition, NIH developed and implemented results modules to accept and display to the public summary results information, including adverse event information from registered trials. Mandatory reporting of results began in September 2008, with mandatory submission of adverse event information following in September 2009. During FYs 2008-2009, more than 34,000 trials were newly registered with ClinicalTrials.gov, raising the total number of registered trials to 80,000. In addition, summary results of more than 830 clinical trials were submitted and made available at ClinicalTrials.gov, with the rate of results submission approaching 200 trials per month by the end of FY 2009. To solicit input on issues to be considered in rulemaking for further expansion of ClinicalTrials.gov, a public meeting was held in April 2009; more than 200 participants attended the meeting, and more than 70 written comments were submitted to a public docket.

→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (I) (**NLM**)

The Biomedical Translational Research Information System: The NIH intramural program uses a wide variety of clinical and research data management systems to gather clinical research data. The single largest system is the Clinical Research Information System (CRIS) at the NIH CC; however, many of the other 26 ICs at NIH have their own systems, as do many laboratories at the ICs and even individual researchers within the laboratories. Thus, research data for individual clinical trials and on individual subjects are scattered across multiple diverse systems. The Biomedical Translational Research Information System (BTRIS) project, initiated in 2008 and made available in 2009, includes a sophisticated data warehouse that currently contains the data on more than 447,000 subjects from 8,800 protocols, gathered from the CRIS system (2004 to present), archived data from CRIS' predecessor system (1976 to 2004), and data from systems at NIAID and NIAAA. BTRIS provides NIH researchers with a user-friendly reporting application to obtain data on subjects in their own protocols from across all these sources. They also are able to perform queries against all data on all research subjects from all clinical trials (in de-identified form), to allow them to ask new questions of the data, look for previously unrecognized correlations, and gain new insights through the reuse of data that NIH has been collecting for the past three decades.

→ For more information, see http://btris.nih.gov
→ (I) (**CC**)

ProtoType: ProtoType is an assisted protocol authoring tool that provides a systematic framework where protocols can be developed and maintained throughout their life cycle. ProtoType includes fully customized documents tailored toward individual Institutional Review Boards (IRBs), taking all the guesswork out of creating a protocol and allowing the investigator to focus on authoring. By capturing the entire authoring process electronically, the protocol can be moved easily between the IC IRB, NIH CC, and other Institutes and investigators while tracking the state of the protocol. Ultimately, ProtoType will be an online archive of all protocols submitted by each principal investigator and will maintain the protocols' histories. Prototype currently has incorporated templates from 4 of the 12 NIH IRBs, with more than 200 distinct investigators using the system.

→ For more information, see https://prototype.cc.nih.gov
→ (I) (**CC**)

Genomic Information Systems: Understanding the Genetic Basis of Disease

Influenza Virus Resources: NIH maintains the Influenza Virus Resource, a database of influenza virus sequences that enables researchers around the world to compare different virus strains, identify genetic factors that determine the virulence of virus strains, and look for new therapeutic, diagnostic, and vaccine targets. The resource was developed using publicly accessible data from laboratories worldwide in addition to targeted sequencing programs such as NIH's Influenza Genome Sequencing Project. Updated daily, this comprehensive sequence resource includes more than 90,000 influenza sequences and more than 2,000 complete genomes. In the spring of 2009, with the rapid emergence of the 2009 H1N1 pandemic, the database received more than 2,200 influenza sequences from publicly accessible databases and included sequences from CDC and labs from 35 countries. By the end of 2009, nearly 10,000 H1N1 sequences were in the database. The combination of extensive sequence data and advanced analytic tools provided researchers worldwide immediate access for investigating the rapid spread of this flu and developing vaccines for combating it. Other influenza virus information resources also were developed in response to 2009 H1N1. To facilitate access to the scientific literature, a pre-formulated search for 2009 H1N1 papers was added to PubMed. A 2009 H1N1 Flu page with comprehensive information on Federal response, international resources, transmission, prevention, treatment, genetic makeup, and veterinary resources was added to Enviro-Health Links, which provides links to toxicology and environmental health topics of recent special interest, including information in Spanish. For the general public, patients, family members, and caregivers, a health topic on 2009 H1N1 flu, in Spanish and English, was added to the MedlinePlus consumer health resource.

- → Bao Y, et al. *J Virol* 2008;82(2):596-601. PMID: 17942553. PMCID: PMC2224563.
- → For more information, see http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html
- → For more information, see http://www.pubmed.gov
- → For more information, see http://sis.nlm.nih.gov/enviro/swineflu.html
- → For more information, see http://www.nlm.nih.gov/medlineplus/h1n1fluswineflu.html
- → For more information, see http://www.nlm.nih.gov/medlineplus/spanish/h1n1fluswineflu.html
- → This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Molecular Biology and Basic Research*
- → (I) (**NLM**)

Genome-Wide Association Studies: With unprecedented speed, researchers have used an approach called genome-wide association studies (GWAS) to explore genetic variants and their complex relationships to human health and disease. GWAS research has linked a stunning number of genetic variants to common conditions—more than 130 in 2008 alone. For example, the obesity epidemic and its related health conditions pose a great challenge for the Nation. In 2008, the Genetic Investigation of Anthropometric Traits consortium identified six genes associated with body mass index, a key indicator for obesity. Also in 2008, three GWAS of lung cancer implicated several genes already known to be linked to nicotine addiction. In a feat that would not have been possible without the power of whole genome analysis, the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium in 2009 gathered data from participants in long-running studies to reveal genetic variants associated with an increased risk of stroke. Identification of genetic variants associated with common diseases opens new windows into the biology of health and disease. This work also raises the possibility of someday using genetic testing, in combination with family history, to identify at-risk, pre-symptomatic individuals who might benefit from personalized screening and preventive therapies.

- → For more information, see http://www.genome.gov/27528559
- → For more information, see http://www.genome.gov/27529231
- → For more information, see http://www.genome.gov/27531390
- → This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
- → (E, I) (**NHGRI, NIDDK, NCI, NIA, NHLBI, NIMH**, NINDS)

Database of Genotype and Phenotype (dbGaP): Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics, and other scientific data, NIH established dbGAP to house the results of genome-wide association studies (GWAS), which examine genetic data of de-identified subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2009, dbGaP included results from more than 40 GWAS, including genetic analyses related to such diseases as Parkinson's disease, ALS, diabetes, alcoholism, lung cancer, and Alzheimer's disease. dbGaP is the central repository for many NIH-funded GWAS to provide for rapid and widespread distribution of such data to researchers and accelerate the understanding of how genes affect the susceptibility to and severity of disease.

→ For more information, see http://view.ncbi.nlm.nih.gov/dbgap
→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*
→ (I) (**NLM**)

Genome-Wide Association Studies of Autoimmune Disease Risk: In recent years, genome-wide association studies (GWAS) have transformed the identification of gene regions related to disease risk, through an unbiased analysis of patients with a disease, in comparison with people who don't have it. These GWAS require large numbers of patients and individuals without the disease to obtain statistically significant results. Long-term NIH support of disease registries and repositories of biological samples have been essential to successful projects, in addition to productive, multisite collaborations across the United States, including international researchers and contributions from the NIH Intramural Research Program. GWAS have yielded important information about disease risk, as well as understanding of disease pathways and potential therapeutic targets, in several autoimmune diseases in the past 2 years. Diseases studied include psoriasis, rheumatoid arthritis, systemic lupus erythematosus (or lupus), ankylosing spondylitis, and type 1 diabetes. Initial results from GWAS require confirmation by replication in additional groups of patients. More detailed localization of disease risk genes can be achieved through comprehensive DNA sequencing of candidate gene regions. New NIH initiatives are supporting these follow-up studies, which are critical to validating GWAS findings.

→ Plenge RM, et al. *Nat Genet* 2007;39(12):1477-82. PMID: 17982456. PMCID: PMC2652744.
Wellcome Trust Case Control Consortium, et al. *Nat Genet* 2007;39(11):1329-37. PMID: 17952073. PMCID: PMC2680141.
Nath SK, et al. *Nat Genet* 2008;40(2):152-4. PMID: 18204448.
Hom G, et al. *N Engl J Med* 2008;358(9):900-9. PMID: 18204098.
Liu Y, et al. *PLoS Genet* 2008;4(3):e1000041. PMID: 18369459. PMCID: PMC2274885.
Nair RP, et al. *Nat Genet* 2009;41(2):199-204. PMID: 19169254. PMCID: PMC2745122.
Barrett JC, et al. *Nat Genet* 2009;41:703-707. PMID: 19430480. PMCID: PMC2889014.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/10_04.asp
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-09-135.html
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2008/Ankyl_Spond_gene.asp
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-123.html
→ For more information, see http://www.nature.com/ng/journal/v41/n6/abs/ng.381.html
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Genomics*
→ (E/I) (**NIAMS**, NCRR, NHGRI, NHLBI, NIAID, NICHD, NIDA, NIDCR, NIDDK)

The National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE): Over the past 20 years, vision researchers have been remarkably successful in identifying the genetic basis of eye disease. More than 400 disease genes causing a wide range of eye diseases have been isolated, revealing unimagined complexity. Although some gene mutations lead to clearly defined clinical characteristics, or phenotypes, many other mutations are clinically indistinguishable from one another. Matching genetic testing with the disease phenotype will help to resolve this complexity and allow clinicians

to diagnose specific diseases more accurately. However, commercial testing for rare eye diseases is limited. eyeGENE will expand the Nation's capacity to genotype patients with eye disease, thus improving patients' knowledge of their condition and the potential to personalize treatment eventually. From a research standpoint, patient DNA samples are invaluable for molecular studies, and patient registries are critical for patient recruitment for clinical trials. To address these needs, the NIH created eyeGENE, a partnership between government, health care providers, private industry, and scientists to broaden research resources and increase patient accessibility to diagnostic genetic testing. eyeGENE will provide researchers with patient genotype and phenotype data to elucidate ophthalmic disease genes and genetic modifiers, and enhance future enrollment of subjects in clinical trials.

→ Brooks BP, et al. *Arch Ophthalmol* 2008;126(3)424-5. PMID: 18332328.
→ For more information, see http://www.nei.nih.gov/resources/eyegene.asp
→ (E/I) (**NEI**)

NINDS Human Genetics Repository: In 2002, NINDS established the Human Genetics Repository to collect, store, characterize, and distribute DNA samples and cell lines and standardized clinical data for the research community. By June 2009, the repository held material from 27,166 subjects, including those with cerebrovascular disease (8,625), epilepsy (1,356), Parkinson's disease (5,700), motor neuron diseases such as amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, (2,631), and Tourette Syndrome (1,185), as well as control samples (6,162). The ethnically diverse collection represents populations from the United States and several other countries. Investigators have submitted or published more than 100 scientific articles based on data from this resource, and technological advances allowing whole genome screening for disease genes also have enhanced its value.

→ For more information, see http://ccr.coriell.org/Sections/Collections/NINDS/?SsId=10
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (E, I) (**NINDS**)

Dietary Supplement Ingredient Database (DSID): Working with the Nutrient Data Laboratory, Beltsville Human Nutrition Research Center, which is part of the USDA Agricultural Research Service, and other Federal agencies, NIH developed the DSID to estimate levels of ingredients in dietary supplement products. The main features of the database include data files, a research summary, and an adult multivitamin/minerals calculator. Since more than half of American adults report taking a dietary supplement, the estimates in the DISD will improve assessment of total nutrient intake from foods and supplements.

→ For more information, see http://dietarysupplementdatabase.usda.nih.gov
→ (E) (**ODP/ODS**)

Dietary Supplement Labels Database (DSLD): NIH is developing a comprehensive information resource on dietary supplements labels. The current database includes information from the labels of approximately 4,000 dietary supplement products in the marketplace, including vitamins, minerals, herbs or other botanicals, amino acids, and other specialty supplements. Ingredients of dietary supplements in this database are linked to other NIH databases such as MedlinePlus® to allow users to investigate the dietary ingredients and view biomedical literature pertaining to them. NIH is piloting the development of a full-scale application that includes label information on virtually all dietary supplements sold in the United States. The future DSLD will provide comprehensive label information in a format that is user-friendly for both consumers and researchers. The information included in the database will be determined by Federal and stakeholder user groups.

→ For more information, see http://dietarysupplements.nlm.nih.gov
→ (E) (**NLM**, ODP/ODS)

Disease Registries and Surveillance Systems: Tracking and Monitoring Disease

Seeking Solutions for People with Sjogren's Syndrome: Sjogren's syndrome is one of the most prevalent autoimmune disorders, affecting as many as 4 million people in the United States. Nine out of 10 patients affected are female. It is an autoimmune disease that progressively destroys salivary and lachrymal glands. The most common symptoms include dry eyes, dry mouth, fatigue, and musculoskeletal pain. A significant roadblock for moving discoveries ahead in the field of Sjogren's syndrome is the lack of data and biospecimens available for research. Recognizing the problem, NIH spearheaded an effort to establish Sjogren's patient registries at two extramural institutions as well as through its own intramural program. These groups are working together to generate and share with the general research community the genome-wide genotyping data and clinical information from the cohorts enrolled through these efforts. This resource should jumpstart efforts to understand genetic contributions to Sjogren's syndrome and the etiologic overlap with related autoimmune conditions such as lupus and rheumatoid arthritis. In addition to participating in the patient registry and genotyping efforts described above, the Sjogren's Syndrome Clinic, located in the NIH CC, collects systematic clinical and laboratory data on the Sjogren's syndrome (and salivary dysfunction) population. Gene therapy and bioengineering hold promise for the repair or even replacement of salivary glands ravaged by Sjogren's syndrome. More than 300 patient visits occur annually, and the clinic is expanding its patient recruitment to accelerate the conduct of clinical trials that might shed light on this disorder.

→ Korman BD, et al. *Genes Immun* 2008;9(3):267-70. PMID: 18273036.
Roescher N, et al. *Oral Dis* 2009;15(8):519-26. PMID: 19519622. PMCID: PMC2762015.
Nikolov NP, Illei GG. *Curr Opin Rheumatol* 2009;21(5):465-70. PMID: 19568172. PMCID: PMC2766246.
→ For more information, see http://www.sjogrens.org/
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Genomics*
→ (E/I) (**NIDCR**, CC, ORWH)

International Epidemiologic Databases to Evaluate AIDS (IeDEA): The goal of the IeDEA program is to conduct analyses based on comparable data from multiple regions and studies. This initiative has established international regional centers for the collection and harmonization of data and has created an international research consortium to address unique and evolving research questions in HIV/AIDS currently unanswerable by single cohorts. High-quality data are being collected by researchers throughout the world. This initiative provides a means to establish and implement methodology to pool the collected data effectively—thus providing a cost-effective means of generating large data sets to address the high-priority research questions. Combination of data collected under various protocols frequently is very difficult and not as efficient as the collection of predetermined and standardized data elements. By developing a proactive mechanism for the collection of key variables, this initiative will enhance the quality cost effectiveness and speed of HIV/AIDS research. Participating regions include Canada and the United States, the Caribbean and Central and South America, Asia and Australia (excluding China), West Africa, Central Africa, East Africa, and Southern Africa.

→ For more information, see http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**NIAID**, NCI, NICHD)

Environmental Polymorphisms Registry: NIH, in collaboration with the University of North Carolina's General Clinical Research Center, has launched a large volunteer DNA banking project named the Environmental Polymorphisms Registry (EPR). The goal of the EPR is to collect DNA samples from 20,000 individuals in the greater Research Triangle Park region of North Carolina through local health care systems, study drives, health fairs, and other means. This area has a

diverse population varying in age, ethnicity, economic and educational backgrounds, and health status. The EPR offers a valuable resource for human genomic studies, especially when compared to anonymous DNA registries. It was designed for scientists to screen for functionally significant alleles and to identify subpopulations of individuals with shared genotypes, and then correlate their genotypes with their phenotypes in a process known as "recruit-by-genotype." The value of the EPR lies in the ability to identify and then re-contact subjects with potentially significant polymorphisms for further study. A unique feature of the EPR is that two distinct populations are solicited, an apparently healthy population recruited from the general population as well as a clinic population recruited from various clinics and hospitals in the area. Individuals in the clinic population have a wide array of medical conditions, and their inclusion in the EPR increases the likelihood of identifying subjects with both the genotypes and phenotypes of interest. These aspects of the EPR give scientists more flexibility in designing follow-up studies while reducing the ascertainment bias that can occur in genetic epidemiology studies when subjects are recruited based on phenotype.

→ This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E/I) (**NIEHS**)

Surveillance, Epidemiology, and End Results (SEER): The SEER program provides essential data that support cancer research across NIH and collaborating agencies and organizations in the United States and around the world. SEER covers approximately 26 percent of the U.S. population, with information in its database on more than 5.7 million cancer cases. SEER registries routinely collect data on patient demographics, primary tumor site, morphology, extent of disease at diagnosis, and first course of treatment. All patients are followed annually for vital status and compilation of survival data. The SEER Program is the only comprehensive source of population-based data in the United States that includes stage of cancer at the time of diagnosis and survival rates by stage. It is the only population-based source of long-term incidence and survival data, having a 35-year history in most of its registries. SEER provides source data for the American Cancer Society Facts & Figures and the Annual Report to the Nation on the Status of Cancer. SEER is one of the most fundamental contributors to the cancer research infrastructure, adding more than 380,000 cases each year. The program sets national benchmarks for incidence and survival rates and is the primary source of reports on cancer death rates. The size of the database allows for analysis of rare cancers and cancer heterogeneity at both the tumor and patient level. The SEER database also includes prevalence information on the 11.4 million cancer survivors in the United States, allowing analysis by age and cancer site as well as time elapsed since diagnosis. There are more than 2,000 agreements executed annually for the public-use data and more than 3 million hits per month on the SEER Internet homepage.

→ For more information, see http://seer.cancer.gov
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NCI**)

Cancer Control P.L.A.N.E.T: The Cancer Control P.L.A.N.E.T. (Plan, Link, Act, Network with Evidence-based Tools) Web portal was launched collaboratively in 2003 by NIH, Agency for Healthcare Research and Quality, American Cancer Society, Centers for Disease Control and Prevention, Commission on Cancer, and Substance Abuse and Mental Health Services Administration. The portal now has been expanded, in collaboration with the Surveillance Action Group of the Canadian Partnership Against Cancer, to include Cancer Control P.L.A.N.E.T. Canada. The Canadian site follows the same design as the U.S. site, while engaging Canadian cancer control practitioners and researchers in usability testing to ensure that the Canadian site meets their needs. Both the Canadian and U.S. sites provide a single point of access to high-quality tools and resources from multiple national organizations that can be used to design, implement, and evaluate evidence-based cancer control plans and programs. They guide local programs to resources that help them determine cancer risk and cancer burden in their geographic areas. They also help identify potential partners and provide online resources for interpreting research findings and recommendations and accessing products and guidelines for planning and evaluation.

→ For more information, see http://cancercontrolplanet.cancer.gov
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NCI**)

A Look at Drug Abuse Trends: Local to International: Two major systems of data collection are helping to identify substance abuse trends locally, nationally, and internationally: Monitoring the Future Survey (MTF) and the Community Epidemiology Work Group (CEWG). Both help to surface emerging drug abuse trends among adolescents and other populations, and guide responsive national and global prevention efforts. The MTF project, begun in 1975, has many purposes, the primary one being to track trends in substance use, attitudes, and beliefs among adolescents and young adults. The survey findings also have been used by the President's Office of National Drug Control Policy to monitor progress toward national health goals. The MTF project includes both cross-sectional and longitudinal formats—the former given annually to 8th, 10th, and 12th graders to see how answers change over time, and the latter given every 2 years (until age 30), then every 5 years to follow up on a randomly selected sample from each senior class. CEWG, established in 1976, provides both national and international information about drug abuse trends through a network of researchers from different geographic areas. Regular meetings feature presentations on selected topics, as well as those offering international perspectives on drug abuse patterns and trends. CEWG findings reported in 2008 and 2009 show decreases in methamphetamine indicators (e.g., treatment admissions), suggesting that the problems that had escalated in the first half of the decade may have stabilized or declined. Development of a Latin American Epidemiology Network is underway. NIH also has provided technical consultation for the planning and establishment of an Asian multicity epidemiological network on drug abuse.

→ For more information, see http://www.monitoringthefuture.org/
→ For more information, see http://www.drugabuse.gov/about/organization/CEWG/CEWGHome.html
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
→ (E) (**NIDA**)

Alcohol Policy Information System: Public policies that affect alcohol consumption and related behaviors can influence a range of health and social outcomes. The NIH has developed the Alcohol Policy Information System (APIS) to provide authoritative and detailed information on alcohol-related public policies in the United States at both the State and Federal levels. Intended primarily as a tool for researchers, the APIS website (http://alcoholpolicy.niaaa.nih.gov), posted in June 2003, features compilations and analyses of alcohol-related statutes and regulations. APIS is designed to simplify the process of ascertaining the state of the law for studies on the effects and effectiveness of alcohol-related policies. APIS currently provides information on 30 specific policy topics, including summary descriptions, maps, detailed comparison tables, and the specific dates on which provisions became or ceased to be effective. For most policy topics, APIS coverage begins as early as January 1, 1998, and extends through September 18, 2008. NIH issued program announcements for alcohol policy research that use APIS in 2007.

→ Fell J, et al. *Alcohol Clin Exp Res* 2009;33(7):1208-1219.PMID: 19389192.
Wagenaar AC, et al. *Addiction* 2009;104(2):179-90. PMID: 19149811.
→ For more information, see http://www.alcoholpolicy.niaaa.nih.gov
→ (E) (**NIAAA**)

Standardized Vocabularies, Data Protocols, and Tools

Health IT Standards and Electronic Health Records: NIH researchers are engaged in developing Next Generation electronic health records (EHRs) with advanced decision-support capabilities to facilitate patient-centered care, clinical research, and public health. As the central coordinating body for clinical terminology standards within HHS, NIH works

closely with the Office of the National Coordinator for Health Information Technology (ONC) to support nationwide implementation of an interoperable health information technology infrastructure. NIH develops or licenses key clinical terminologies that are designated as standards for U.S. health information exchange. The Unified Medical Language System Metathesaurus, with more than 8.1 million concept names from more than 125 vocabularies, is a distribution mechanism for standard code sets and vocabularies used in health data systems. NIH also produces RxNorm, a standard clinical drug vocabulary; supports the LOINC nomenclature for laboratory tests and patient observations; and collaborates with the International Health Terminology Standards Development Organisation to promote international adoption of the SNOMED CT clinical terminology. In FY 2009, NIH released the first version of the CORE Problem List Subset of SNOMED CT, designed to facilitate coding of problem list data in EHRs by mapping frequently used terms from seven large-scale health care institutions to corresponding SNOMED CT concepts. The Newborn Screening Codes and Terminology Guide, a Web portal to support more effective use of newborn screening laboratory test information, was created in FY 2009 in collaboration with ONC, the Health Resources and Services Administration, and newborn screening organizations.

→ For more information, see http://www.nlm.nih.gov/research/umls
→ This example also appears in Chapter 3: *Technology Development*
→ (I) (**NLM**)

Health Information Technology: Health information technology research that enables the integration of clinical data and medical image diagnostic and treatment data with the patient's medical history in a comprehensive electronic medical record will improve clinical decision-making. The ability to connect and exchange diagnostic information and medical images between health care providers, clinics, and hospitals will help provide the timely information that is needed for effective health care and will help reduce unnecessary, excessive, and duplicative procedures. A patient-centered approach to comprehensive electronic health records will allow patients access to their health information. This will enable patients to play an active role in their own wellness by enabling them to ask knowledgeable questions about treatment options. Additionally, patients also are empowered to provide this information to any and all health care providers as needed, independent of their location or where the medical data was created or stored. NIH supports research in new methods and technologies to address issues such as: interoperability of data systems, compatibility of computer software across medical institutions, security of data during transmission, HIPAA compliance, availability of affordable data systems for patient care providers, and integration of medical decision-support information in medical data systems.

→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NIBIB**, NLM)

Discovery Initiative for Entrez Databases: The Discovery Initiative aims to maximize the utility of NIH biomedical data resources by better exploiting their inter-linkages. For example, a PubChem record on a chemical structure might link to records for similar proteins, related protein structures, and relevant journal articles. Such linkages provide users with tremendous opportunities for exploration and scientific discovery, but are underutilized currently. The Discovery Initiative aims to improve the retrieval and presentation of results so that users are drawn more readily to related data that could lead to serendipitous discoveries. Improvements have been made in the search interface through the use of "sensors" that can detect certain categories of search terms automatically, such as genes or drugs, and then direct the user's attention to resources that may augment the original search. Through these linkages, users are better able to traverse the 40-plus databases in the Entrez network, ranging from topics such as human genetic disorders and genome projects to cancer chromosomes and protein structure.

→ National Center for Biotechnology Information. Featured Resource: Improvements to NCBI Services Promote Discovery. *NCBI News* 2009;February:1.
→ (I) (**NLM**)

Collective Intelligence for Knowledge Discovery: NIH has started a new NIH initiative in collective intelligence. The goal is to create deep repositories of knowledge backed by controlled vocabularies or ontologies, and to create or enhance semantically interoperable applications capable of discovering knowledge hidden within these repositories. Current applications such as the Human Salivary Proteome Annotation System, the Common Assay Reporting System, and the caBIG Protocol Lifecycle Tracking Tool are among the initial steps of a knowledge infrastructure. These applications harvest the collective knowledge of targeted scientific communities to store protocols, data, and results. Other tools developed for this initiative (e.g., the context-sensitive text mining system for identification of high-risk, high-reward research) use statistical natural language processing to discover new knowledge, such as, whether in peer review, an application for funding was considered high-risk and high-reward. Additional pilot studies are evaluating computational linguistics and knowledge management tools for biomedical and clinical informatics, portfolio analysis, systems biology, proteomics, genomics, and knowledge representation paradigms. The collective-intelligence initiative will lead to a knowledge infrastructure that can shift the paradigms of data re-use and knowledge discovery dramatically.

→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (I) (**CIT**, CC, NCI, NHGRI, NIDCR, NIMH, OD)

NIH Federated Identity Service: NIH Federated Identity Service enables people from institutions external to NIH to collaborate by allowing them to use their user name or password from their home organization to access authorized NIH systems. Federated Identity maintains user privacy by keeping the users' credentialing process within their home organization while enabling more seamless collaborations and transactions between federated organizations that can trust each other's identity authentication. Federated Identity Service currently federates with more than 22 institutions, including its sister operational division, the FDA, and universities such as Johns Hopkins, Duke, and Ohio State. NIH made its Clinical & Translational Science Awards (CTSA) Wiki one of the first NIH systems to be federated with nongovernment institutions. Federated Identity facilitates access to the wiki—an online, authorized access, collaborative work environment for members of the CTSA Consortium, which currently supports 1,200 members at 38 universities. The CTSA program reports that 15 of their awarded institutes actively federate with NIH. Other services accepting external credentials through Federated Identity include the website NCRR Annual Progress Report Scientific Information System, FDA ITAS Time and Attendance, NLM NCBI SharePoint for Genome Research, and the Salivary Proteome Wiki. In addition to accepting external accounts, NIH users may use their username and password to access such diverse services as GovTrip, the CTSA Indiana University Wiki, and the Genome Browser at University of California Santa Cruz.

→ (I) (**CIT**)

Large-Scale Informatics Infrastructure

The Cancer Biomedical Informatics Grid® (caBIG®): The caBIG® initiative connects researchers and institutions to enable collaborative research and personalized, evidence-based care. More than 1,500 individuals representing more than 450 government, academic, advocacy, and commercial organizations have collaborated to develop a standards-based grid infrastructure (caGrid) and a diverse collection of interoperable software tools, enabling basic and clinical researchers to speed the translation of information from bench to bedside. Forty-nine of the 65 NCI-designated Cancer Centers and 8 of 10 organizations of the NCI Community Cancer Centers Program are actively deploying caBIG® tools and infrastructure in support of their research efforts. Additionally, caBIG® technology is adapted to power noncancer research initiatives such as the CardioVascular Research Grid. Ongoing collaborations with research and bioinformation organizations in the United Kingdom, China, and India are driving international adoption of caBIG® resources. The caBIG® infrastructure also supports a new health care ecosystem, BIG Health™, in collaboration with various stakeholders in biomedicine (e.g., government, academia, industry, nonprofits, and consumers) in a novel organizational framework to demonstrate the feasibility and benefits of personalized medicine. BIG Health™ will provide the foundation for a new approach in which clinical care, clinical research, and scientific discovery are linked.

→ For more information, see http://cabig.cancer.gov
→ For more information, see http://bighealthconsortium.org/
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*
→ (E/I) (**NCI**)

Biomedical Informatics Research Network (BIRN): Modern biomedical research generates vast amounts of diverse and complex data. Increasingly, these data are acquired in digital form, allowing sophisticated and powerful computational and informatics tools to help scientists organize, store, query, mine, analyze, view, and, in general, make better use and sense of their data. Moreover, the digital form of these data and tools makes it possible for them to be shared easily and widely across the research community at large. NIH has supported development of the BIRN infrastructure to share data and tools by federating new software tools or using the infrastructure to federate significant datasets. BIRN fosters large-scale collaborations by using the capabilities of the emerging national cyberinfrastructure. In FY 2009, the BIRN Coordinating Center transitioned to a new home at the University of Southern California. The new BIRN Coordinating Center uses grid computing technology to create a virtual organization for basic and clinical science investigators across the network. In addition, a new BIRN Community Service (U24) grant was awarded to help expand the BIRN user community to researchers and clinicians beyond the neuroscience and imaging fields.

→ For more information, see http://www.ncrr.nih.gov/birn
→ For more information, see http://www.nbirn.net
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NCRR**)

A Clearinghouse for Neuroimaging Informatics Tools and Resources: Many neuroimaging tools and databases are underutilized because they cannot be found easily, are not user-friendly, or are not easily adoptable or adaptable. In an effort to promote the enhancement, adoption, distribution, and evolution of neuroimaging informatics tools and resources, the NIH Blueprint for Neuroscience Research has launched the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC). Examples of included tools are: image segmentation, image registration, image processing pipelines, statistical analysis packages, spatial alignment and normalization algorithms, and data format translators. Resources include: well-characterized test datasets, data formats, and ontologies. Since the first release in October 2007, the clearinghouse website, or NITRC, has become host to 180 tools and resources, with a community of 13,602 unique visitors who downloaded NITRC tools and resources, and 7,000 unique visitors per month, more than 954 of which are registered users (11 percent non-English speaking). The hits to the site have reached 15,635,019/month. Since its inception, more than 50,000 software files have been downloaded. More than 53 percent of the tools on NITRC had not been shared online previously but now are available to the community. In 2009, the NITRC project won the first place of Excellence.gov awards, the largest Federal government award program to recognize the very best in government IT programs, among 61 competitors. Through the initiative, nearly 40 awards have been made to neuroimaging tools and resource developers to enhance the accessibility, interoperability, and adoptability of their existing tools and resources.

→ Ardekani BA, Bachman AH. *Neuroimage* 2009;46(3):677-82. PMID: 19264138. PMCID: PMC2674131.
→ For more information, see http://www.nitrc.org/
→ For more information, see http://neuroscienceblueprint.nih.gov/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*
→ (E) (**NIH Blueprint**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

National Centers for Biomedical Computing: There are seven NIH Roadmap National Centers for Biomedical Computing (NCBC). Funded as cooperative agreements, these centers collectively cover broad areas of neuroinformatics, functional genomics, image post processing, multiscale modeling, cellular pathways, semantic data integration and ontologies, information networks, cellular networks and pathways, clinical informatics, disease-gene-environment analysis, and clinical decisions support.

→ For more information, see http://ncbcs.org/
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
→ (E) (**NIGMS**, Common Fund - all ICs participate)

Disaster Information Services: A Disaster Information Management Research Center was established in FY 2008 with the aim to facilitate access to disaster information, promote more effective use of libraries and disaster information specialists in disaster management efforts, and ensure uninterrupted access to critical health information resources when disasters occur. A disaster information website provides access to a broad range of emergency preparedness and response information. The Center also collaborates with the Navy National Medical Center, Suburban Hospital, Johns Hopkins Medicine, and NIH CC in the Bethesda Hospital Emergency Preparedness Partnership to provide backup communication systems and develop tools for patient tracking, information sharing and access, and responder training and to serve as a model for hospitals across the Nation. NIH also develops advanced information services and tools to assist emergency responders when disaster strikes. WISER (Wireless Information System for Emergency Responders) was developed for use during hazardous materials incidents and is available on the Internet or for downloading onto PDAs and PCs. Usage continues to grow, with more than 47,000 downloads onto PDAs in FY 2008. Radiation Event Medical Management (REMM) is a downloadable toolkit for use by health care providers during a mass casualty radiation event, with a version for mobile platforms released in FY 2008. Developed in collaboration with the HHS Office of Public Health Preparedness, REMM includes procedures for diagnosis and management of radiation contamination and exposure, guidance for use of radiation medical countermeasures, among other features to facilitate medical responses to radiation emergencies.

→ For more information, see http://disasterinfo.nlm.nih.gov
→ For more information, see http://wiser.nlm.nih.gov
→ For more information, see http://remm.nlm.gov
→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (I) (**NLM**)

Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer Care: The purpose of the Cancer Research Network (CRN) is to enhance research on cancer epidemiology, prevention, early detection, and control in the context of health care delivery systems. CRN combines established research groups affiliated with 14 health care delivery organizations that provide comprehensive care to a racially and ethnically diverse population of nearly 11 million individuals. CRN has developed strong research capabilities in several areas: developing and applying innovative methods to collect and interpret data from both conventional and electronic medical records systems; assembling large samples of patients with documentation of patient characteristics and longitudinal data on receipt of health services and clinical and quality-of-life outcomes; collecting and integrating complex data from patients, providers, and organizations to examine issues in health care delivery from multiple perspectives; quantifying the effect of key factors in the delivery process that may determine quality and outcomes of care; and conducting studies on behavioral and systems-based interventions to improve the delivery of care in community-based health care delivery systems. The Breast Cancer Surveillance Consortium (BCSC) is a research resource for studies designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. The BCSC is a collaborative network of seven mammography registries with linkages to tumor and/or pathology registries. The Consortium's database contains information on 7,521,000 mammographic examinations, 2,017,869 women, and 86,700 cancer cases.

→ For more information, see http://crn.cancer.gov
→ For more information, see http://breastscreening.cancer.gov/
→ This example also appears in Chapter 2: *Cancer*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Clinical and Translational Research*
→ (I) (**NCI**)

CISNET—A Resource for Comparative Effectiveness Research: The Cancer Intervention and Surveillance Modeling Network (CISNET) represents a quantum leap forward in the practice of modeling to inform clinical and policy decisions. While contemporary science has enabled the collection and analysis of health-related data from numerous sectors, enormous challenges remain to integrate various sources of information into optimal decision-making tools to inform public policy. Collaborative work on key questions promotes efficient collecting and sharing of the most important data and critical evaluation of the strengths and weaknesses of each resource. Providing results from a range of models, rather than a single estimate from one model, brings credibility to the process and reassures policymakers that the results are reproducible. CISNET is a consortium of NIH-sponsored investigators who use modeling to improve understanding of the impact of cancer control interventions (e.g., prevention, screening, and treatment) on incidence and mortality trends. The consortium's work informs clinical practice and recommended guidelines by synthesizing existing information to model gaps in available knowledge. CISNET provides a suite of models that are poised to determine the most efficient and cost-effective strategies for implementing technologies in the population. Four groups of grantees focus on breast, prostate, colorectal, and lung cancers using statistical simulation and other modeling approaches. Their models incorporate data from randomized controlled trials, meta-analyses, observational studies, epidemiological studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of these interventions.

→ For more information, see http://cisnet.cancer.gov/
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Research*
→ (E/I) (**NCI**)

NIH Biowulf Cluster Enables Large-Scale Biomedical Research: The Biowulf cluster provides NIH researchers with a world-class supercomputer that enables the conduct of large-scale biomedical computational projects, allowing scientific research that otherwise would not be possible. Biowulf comprises more than 6,000 interconnected processors operating cooperatively to solve such diverse problems as: identifying genotype patterns of variation across worldwide human populations; validating algorithms used in computer-aided detection of colon polyps ("Virtual Colonoscopy"); computing the molecular structures of viruses such as HIV using 3D electron microscopy; facilitating whole-genome assembly and genome-wide association studies resulting from next-generation DNA-sequencers; and, as part of the NIH Roadmap Initiative for Molecular Libraries, generating conformation ensembles for 25 million chemical structures. In 2008-2009, more than 105 scientific papers published by NIH intramural scientists cited the use of Biowulf as a computational resource.

→ This example also appears in Chapter 3: *Technology Development*
→ (I) (**CIT**)

Biomedical Informatics Research and Training

Informatics Research Training Programs: Exploiting the potential of information technology to augment health care, biomedical research, and education requires investigators who understand biomedicine as well as knowledge representation and decision support. NLM is the principal source of extramural funding for research training in the fields of biomedical informatics, supporting approximately 270 trainees at 18 institutional training programs throughout the country. NLM also provides intramural informatics research training opportunities for another 70 students, postdoctorates, and visiting scientists, as well as training and career development fellowships for health science librarians on the NIH campus and at academic health sciences centers across the country. Collectively, NLM's research training programs

encompass health care informatics, bioinformatics, clinical research translational informatics, and public health informatics. Recent highlights and developments in informatics training include:

- A congressional supplemental appropriation for FY 2008 allowed NIH to add 26 NLM training slots.
- A Diversity Short-Term Trainee Program was implemented to improve the diversity of informatics trainees, with funding for 18 trainees at 7 training programs.
- Funds from the American Reinvestment and Recovery Act were committed to support an additional 56 2-year slots at 10 of its informatics training programs.
- A new Clinical Informatics Postdoctoral Fellowship was established to attract young physicians to NIH to pursue research in informatics.

→ For more information, see http://www.nlm.nih.gov/training.html
→ This example also appears in Chapter 3: *Research Training and Career Development*
→ (E/I) (**NLM**) (ARRA)

Technology Development

By 2030, 72 million Americans will be 65 years old or older. The strain that this population will put on the health care system will be broad-based, but critical care settings in particular—especially intensive care unit (ICUs)—will face significant challenges. ICU care succeeds in part by intensive monitoring of a patient's changing condition. However, keeping track of that level of detail, especially in a busy unit, can slow treatment decisions, and in some cases, lead to errors. A team of NIH-funded researchers sees an opportunity to improve the efficiency, accuracy, and timeliness of clinical decision-making in the intensive care setting. They are developing an ICU patient monitoring system that not only will track vital signs in real time but also will model and predict potential clinical outcomes given various scenarios. Clinicians and researchers also will use this multiparameter intelligent monitoring in intensive care (MIMIC) system as a knowledge base with open access to further develop and test computer models that may improve care.

Introduction

NIH support of technology development continues to trigger revolutions in the understanding of health and disease. In recent years, biotechnology and nanotechnology have undergone extensive technology development. Biotechnology combines disciplines such as genetics, molecular biology, biochemistry, embryology, and cell biology, which in turn are linked to disciplines such as information technology, robotics, and bioengineering to enable the development of new or enhanced tools and devices to further basic scientific research as well as lead to improvements in human health. Nanotechnology research takes advantage of the phenomenon that the properties of some materials change significantly at very small scales, often with surprisingly useful consequences. NIH-supported nanotechnology research exploits this phenomenon in efforts to develop devices with unique features for diagnosing and treating disease. It is a highly multidisciplinary field, drawing from fields such as applied physics, materials science, supramolecular chemistry, and mechanical and electrical engineering.

Examples of FYs 2008 and 2009 NIH-supported technology development research include:

- A microchip to identify cancer cells circulating throughout the body
- "Medical GPS" to navigate through the body, find cancer cells within a tumor, destroy them, and deliver chemotherapy
- Hand and arm prosthesis systems controlled by intact muscle recordings that produce fine finger movements and offer feedback on position and force
- A lensless microscope that fits into a cell phone and assists with remote bedside monitoring
- Innovative high-throughput methods for detecting and characterizing disease-causing alterations in genes and proteins
- A new system of biomaterials that reprograms cells in the body to fight cancer
- Smart coatings for implants that mimic human tissue

Technology development critical to research on a specific disease, organ system, life stage, or field is supported by the relevant NIH Institute. For example, NCI supports the development of technology necessary to more effectively diagnose and treat cancer. NIEHS supports research on how environmental exposures affect human health and actively develops technology that facilitates understanding of how the environment influences the development and progression of human disease.

In addition, NIBIB and NCRR support broad areas of technology development and application, including infrastructure. They also support interdisciplinary research aimed at developing fundamental platform technologies that can be translated into several biomedical applications. This work sometimes is done in collaboration with a disease-specific Institute as the work moves closer to clinical application.

Many of the core challenges in today's research require technologies, databases, and other scientific resources that are more sensitive, robust, and easily adaptable to unique applications than existing technologies. This is especially true in order to develop a more detailed understanding of the vast networks of molecules that make up cells and tissues, their interactions, and their regulation; to develop a more precise knowledge of the combined effects of environmental exposures, individual susceptibility, and molecular events at the onset of disease; and to capitalize on the completion of the human genome sequence and recent discoveries in molecular and cell biology. Moreover, wide access to such tools is important. In 2002, NIH recognized that a gap existed in the support of crosscutting technology development essential to creating such tools. In response, the NIH Roadmap theme New Pathways to Discovery was initiated to advance understanding of biological systems and build a better "toolbox" for medical research in the 21st century. The NIH Roadmap is supporting the development of these resources through five components of the New Pathways to Discovery theme, including Building Blocks, Biological Pathways, and Networks; Molecular Libraries and Molecular Imaging; Structural Biology; Bioinformatics and Computational Biology; and Nanomedicine.

NIH supports technology development through several complementary approaches, including:

- High-risk, innovative projects with very little preliminary indication of the likelihood of success but a potentially significant impact. These projects usually have small budgets and short timeframes, aimed at proof-of-principle.
- Research project grants with a sound basis in preliminary data, directed at development of a particular technology; some projects may take only a few years while others continue for a decade or more.
- Bioengineering research partnerships, which bring together multiple disciplines such as engineering, cell biology, physics, and neurology to develop solutions to specific biomedical questions or diseases.
- Specialized centers that represent a critical mass of expertise and technology, in which multidisciplinary development of complex, often unique technologies is pursued, typically in the context of challenging research problems that cannot be approached with existing tools.
- Small business grants through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs foster highly innovative projects to bring technological advances into the marketplace for the broadest possible availability and impact. These programs allow NIH to leverage the unique resources and perspectives available in the private sector to complement the work done at universities and the NIH intramural program.

Summary of NIH Activities

The research pipeline is replete with examples of NIH's commitment to technology development, its foresight in identifying emerging needs and promising areas of investigation, and its ability to foster the development of technology that links basic research with clinical applications. The following is an overview of technology development activities at NIH.

Diagnostic and Point-of-Care Technologies

Ideally, patients would have access to high-quality and consistent health care regardless of where they live. Realizing this vision necessitates the development of portable, reliable, and inexpensive equipment. To achieve this also will require the leveraging of technologies developed in other fields, such as telecommunications. Advances in fiber-optic and wireless communications devices allow physicians to engage in telemedicine, that is, the transmission via the Internet of medical information, to deliver health care by communicating with other physicians or pathologists thousands of miles away.

NIH currently funds the Point-of-Care Technologies Research Network, a network of four centers that are developing new point-of-care technologies for early and rapid detection of a wide variety of serious conditions such as neurological emergencies, sexually transmitted diseases, multi-pathogen detection for national disaster preparedness, and diagnosis of infections. These technologies are being designed for use in low-resource settings among underserved populations. The network emphasizes collaboration between front-line health care workers and technology developers so that appropriate tools are created to meet clinical needs.

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Point-of-care technologies for use in pathology laboratories, emergency rooms, doctors' offices, and homes will be a key component of the evolving health care system. Current devices, developed largely with NIH support, range from handheld glucose monitoring systems used by diabetics to monitor their blood sugar levels to laptop-sized ultrasound scanners. Among the technologies on the horizon is a lens-free optical microscope about the size of a dime. The device could be inserted into a cell phone and used as a diagnostic device in rural settings or developing countries, for example in diagnosing malaria. The cost of an individual unit would be about $10.

Another new device has the potential to save eyesight. Born of collaboration between researchers at NIH and NASA, a dynamic light scattering probe detects and quantifies a protein in the eye that is critical to keeping the eye's lens clear. Age-related cataracts develop because too little of the protein, alpha crystallin, is present in the eye. The new probe will be used to monitor the effects of cosmic radiation on astronauts' eyes as well as to study the effects of aging on earth-bound eyes. Early detection of alpha crystallin depletion could lead to treatments that could delay or eliminate the need for cataract surgery.

Although treatment outcomes for primary cancers have improved in the last decade, many deaths occur as a result of the cancer spreading. Body scans can detect distant cancers but often only after the cancer has begun its destructive work. NIH-supported researchers have created a microchip able to detect circulating tumor cells (CTC) in whole blood. This means that from a sample of a patient's blood the microchip identifies specific cancer cells that are spreading through the body via the circulatory system. Clinicians can then make treatment decisions for specific patients based on the molecular and genomic information provided by the CTC analysis.

NIH-supported researchers have created a microchip able to detect circulating tumor cells in whole blood.

E-Health and Biomedical Information Technology

Harnessing the power of the Internet will create unprecedented access to health care information in patient files as well as to raw research data from clinical trials. For health science researchers, shared virtual libraries provide access to data and images from hundreds of studies in various fields. Devising the infrastructure to support a seamless end-user environment requires the collaboration of a host of professionals in computer science, medicine, records management, and other related fields.

NIH-supported efforts are affecting how health care providers, patients, and researchers will use information technology in the future. One such endeavor allows patients to access their own health information. Complete access to diagnostic results and treatment details will permit patients to play an active role in their own health care decision-making by asking more informed questions about their care. Patients will be able to provide this information to any health care provider regardless of where they are located. NIH supports research to ensure that the data are secure during storage and transmission and to address compliance with the Health Insurance Portability and Accountability Act. Benefits of this approach include a reduction in medical errors and elimination of duplicative diagnostic procedures.

Next-generation health care will offer consumers ultrasensitive technologies and techniques to assess normal and diseased states of the body coupled with quick access to vast amounts of health-related data. New modes of collecting patient information, such as the patient-reported outcomes measurement information system (PROMIS), will affect how patients provide information on their conditions and how doctors use that information in treatment decisions. A Web-based computer adaptive testing system, PROMIS will record patient reports on symptoms such as pain, fatigue, and emotional

distress related to various chronic diseases. Other programs that take advantage of the Internet include Positive Choice, a program to reduce risky behaviors that lead to the spread of HIV.

Databases and information clearinghouses are vital tools that allow investigators to streamline their research efforts. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3).The Chemical Effects in Biological Systems (CEBS) Knowledge Base is one such tool that provides data on how different chemicals affect various species. The data, deposited by researchers from industry, government, and academia, assists in understanding how exposures to various substances affect a person's health.

One of the most popular NIH clearinghouses is the Clearinghouse for Neuroimaging Informatics Tools and Resources (NITRC). In the 2 years since its launch, the NITRC has averaged 7,000 visitors per month, provided 50,000 software downloads, and has nearly 1,000 registered users. In 2009, the project won First Place in the Excellence.gov awards, which recognize the very best in government IT programs.

In the 2 years since its launch, the Clearinghouse for Neuroimaging Informatics Tools and Resources has averaged 7,000 visitors per month, provided 50,000 software downloads, and has nearly 1,000 registered users. In 2009, the project won First Place in the Excellence.gov awards, which recognize the very best in government IT programs.

Another resource for collaborative work is the Cancer Biomedical Informatics Grid® (caBIG®), which offers a wide range of software tools to help basic and clinical scientists translate their findings from laboratory to clinic. The caBIG® approach has been adapted to non-cancer research including the Cardiovascular Research Grid. International partners are assisting in dissemination of the technology worldwide community.

To harness the power of computers, NIH supports the Biowulf cluster, a world-class supercomputer that provides intramural researchers with the ability to conduct large-scale biomedical computational projects. Biowulf comprises more than 6,000 interconnected processors operating cooperatively to solve such diverse problems as identifying genotype patterns of variation across human populations worldwide; validating algorithms used in computer-aided detection of colon polyps in "virtual colonoscopy"; computing the molecular structures of viruses such as HIV using 3-dimensional electron microscopy; facilitating whole-genome assembly and genome-wide association studies resulting from next-generation DNA sequencers; and, as part of the NIH Roadmap Initiative for Molecular Libraries, generating structural information for 25 million chemical structures.

To harness the power of computers, NIH supports the Biowulf cluster, a world-class supercomputer that provides intramural researchers with the ability to conduct large-scale biomedical computational projects.

Gene Sequencing and Beyond

The sequencing of the human genome generated excitement in the scientific community. It gave researchers a new way to analyze the function of cells, tissues, and systems in the body to better understand the causes of disease. As more is learned about the genetic contributions to disease, DNA sequence information will become an important tool for individuals and health care providers to evaluate individualized outlooks for disease risk and to improve the prevention, diagnosis, and treatment of disease. However, to deliver genetic information to individuals on a much wider basis, significant decreases must be made in the cost and time needed to sequence an entire human genome. Rapid gains have been made on this front since the start of the Human Genome Project and costs continue to fall dramatically. NIH supports technology development to make genome sequencing more affordable and genomic information a routine part of health care. For example, NIH-supported researchers are conducting studies to discover the molecular mechanisms underlying complex diseases like addiction, which is strongly influenced by genetics. Investigators studying various neurological and psychiatric illnesses already have linked certain genes with specific diseases using custom screening tools known as "gene

chips." Applying these tools to addiction and other brain disorders advances understanding of not only vulnerability to addiction and its comorbidities, but also of ways to target treatments based on an individual's genetic profile. (Also see the section on *Genomics* in Chapter 3.)

Image-Guided Interventions

To detect disease in its earliest stages, and thereby preempt it before symptoms appear, clinicians will need to examine smaller, more localized areas of the body. Image-guided interventions (IGI)—treatments or procedures that precisely target areas within the body with the aid of imaging techniques such as MRI, computed tomography (CT), or ultrasound—enable clinicians to look beneath the surface anatomy to visualize underlying pathology. As a result, images can be used to navigate the anatomy for biopsy and treatment of disease. In addition to diagnosing at-risk individuals, IGI may offer a safer, less-invasive approach to many surgical procedures. Compared with traditional open surgery, minimally invasive procedures result in less tissue trauma, less scarring, and faster postoperative recovery time, which translates into shorter hospital stays and a more rapid return to family and work.

NIH's new Center for Interventional Oncology is leading the way in developing and disseminating innovative cost-effective alternatives to open surgery. Physicians can navigate through the body using "medical GPS"—real-time imaging such as magnetic resonance, computed tomography, or ultrasound. Once at the desired location, the physician can insert a needle into a tumor, deliver heat to destroy it, and then deposit a drug to wipe out residual cancer cells. The center also is pioneering new image-guided approaches to track personalized responses to new drug therapies over time. These endeavors are contributing to the future of personalized medicine.

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Imaging Biological Systems

Better tools and techniques to understand activities within cells, tissues, and organ systems enable researchers to probe deeper to gain an understanding of the biological systems and networks that control both normal function and diseased states. For example, two NIH intramural research groups are collaborating to develop a next-generation MRI system to examine the human brain. The system uses a 7-tesla magnet to produce highly detailed images that reveal structures not visible using conventional MRI.

More detailed information about the body's internal organs is critical to detecting early stages of disease. Finding new ways of using current MRI systems can advance safer diagnostic methods. In the case of liver disease, biopsies may cause pain, result in missed work, and also carry a risk of bleeding. NIH-supported researchers have developed a non-invasive way to assess the liver using MRI and shear waves, a special type of sound wave. With MRI the researchers capture snapshots of the shear waves as they propagate through liver tissue. A computer program translates the waves into a map of the liver that displays the stiffness of the organ. Stiffness indicates disease while suppleness indicates healthy tissue. This could provide a safer alternative not only for liver biopsy but also for diagnosis of cancer in the breast, prostate, and kidney.

Investments in Infrastructure

Advances in the development of new technology cannot come without supporting the infrastructure that undergirds the research endeavor. To that end, NIH supports a Shared Instrumentation Grant and High-End Instrumentation Program, which provides new generation technologies to groups of NIH-supported extramural investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants.

NIH, through additional funding provided by the American Recovery and Reinvestment Act, also is supporting the improvement of facilities for basic and clinical research around the United States to meet the research, training, and support needs of colleges, universities, and other institutions. The Extramural Research Facilities Improvement Program awards grants to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities for biomedical and behavioral research.

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Insights from Animal Models

Another key tool in discovering how a gene or protein malfunctions and causes disease is the use of animal models of disease. Over the last 25 years researchers have bred countless animals with deliberately altered genes that serve as models for studying normal and disease states. These "transgenic" animal models are assisting in fundamental research for a broad range of diseases and conditions. For example, NIH-supported scientists have developed various animal models of human cancer including breast, colon, lung, and others. These models are being used in cancer drug development to answer fundamental questions of drug pharmacology and toxicity. This knowledge is essential to the design of Phase I clinical trials in which the safety, dose level, and response to a new drug are studied in humans.

The models also provide new insights into serious medical conditions such as sepsis, spinal cord injury, and hearing and balance disorders. Sepsis is a serious medical condition caused by a bacterial infection and is a leading cause of illness and death in the United States and worldwide. New treatments for sepsis are on the horizon because of successful studies in animal models. In one study, NIH-supported researchers induced sepsis in an animal model and then infused the blood with bone marrow stromal cells (known to mediate the body's immune response). The stromal cells weakened the body's inflammatory response, thereby lessening the negative effects of sepsis. This opens up the possibility of preparing and storing stromal cells for patients at risk of developing sepsis.

New treatments for sepsis are on the horizon because of successful studies in animal models.

NIH-supported researchers also are using mouse models to study how injected peptide amphiphiles (molecules with water-soluble and water-insoluble properties) self-assemble into minute fibers (nanofibers) that inhibit glial scar formation following spinal cord injury and promote regeneration of both motor fibers and sensory fibers.

Mouse models of hereditary hearing impairments have been instrumental in mapping and cloning many of the deafness genes in humans. These animal models offer researchers many opportunities to study deafness, hereditary factors involved in hearing loss, and genes that are critical for the development and maintenance of the human ear. (Also see the section on *Molecular Biology and Basic Sciences* in Chapter 3.)

Large-Scale Collaborative Activities

The Biomedical Technology Research Centers (BTRCs) and Biotechnology Resource Centers supported by NIH serve a unique purpose in the broad context of NIH-funded research. They represent a critical mass of technological and intellectual resources with a strong focus on service and training for outside investigators. They develop new technologies and tools in areas including tissue engineering, biomaterials, neural communication technologies, imaging, informatics, synchrotrons, electron microscopy, proteomics and glycomics, optics, lasers, and BioMEMS (microelectromechanical systems—technology just above nano-size—that manipulate, analyze, and measure biological or chemical materials). Access to these technologies is critical to enabling research, yet they are frequently too advanced or expensive to be widely available. In FY 2009 there were approximately 70 of these centers located throughout the country that disseminate

and promote the application of such cutting-edge technologies. These technologies are developed across the full spectrum from bench to bedside. These centers are multidisciplinary and collaborative and serve as catalysts for integrating the diverse efforts of NIH-supported researchers, and providing technological infrastructure, experimental and computational resources, and expertise.

The Biomedical Technology Research Centers and Biotechnology Resource Centers represent a critical mass of technological and intellectual resources. They develop new technologies and tools in areas including tissue engineering, biomaterials, neural communication technologies, imaging, informatics, synchrotrons, electron microscopy, proteomics and glycomics, optics, and lasers.

The goal of the NIH-funded Biomedical Informatics Research Network (BIRN) is to allow researchers to collaborate by sharing data and tools. The BIRN is developing the informatics infrastructure necessary to allow any group of investigators to share data among themselves or with a broader community (also see the section on *Disease Registries and Other Data Systems* in Chapter 3). The resulting collaborative environment extends beyond the boundaries of individual laboratories to enable collaborations that cross geographic and disciplinary boundaries. Basic and clinical investigators are able to share disparate data as well as powerful new analytical tools and software across animal models and among multiple sites. This major initiative was developed to allow neuroimagers to share data and tools, but the infrastructure is generic and therefore applicable to other disciplines.

The goal of the NIH-funded Biomedical Informatics Research Network is to allow researchers to collaborate by sharing data and tools.

The Center for Human Immunology, Autoimmunity, and Inflammation (CHI) is a new trans-NIH intramural initiative designed to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiologies, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease. CHI provides unique specific technologies, including flow cytometry to analyze immune cells; high-throughput systems technologies involving the use of new methods for large-scale examination of biological entities ranging from genes to enzymes; and advanced biostatical and computer modeling methods. These technologies often are unavailable to individual laboratories because of cost, complexity, and novelty.

Another technology-intensive collaborative endeavor has developed due to the rapid expansion of the dietary supplement marketplace. This expansion has resulted in a proliferation of ingredients and products and has overtaken the development of reliable analytical methods. Precise, accurate, and rugged analytical methods and reference materials are essential for verification of ingredient identity and measuring the amounts of declared ingredients in raw materials and finished products. Also, dietary supplement labels are required to list certain facts about product identity and content and to be truthful and not misleading. That this is not always the case is due, in part, to the lack of proven and agreed-upon methods to precisely assess the quantity of constituents of many supplements and supplement ingredients. NIH's congressionally mandated Analytical Methods and Reference Materials program is intended to assist in providing these critical tools for quality assurance. NIH is partnering with the Food and Drug Administration and the National Institute of Standards and Technology to promote the development, validation, and dissemination of analytical methods and reference materials for commonly used dietary supplement ingredients.

Multidisciplinary and Interdisciplinary Research

Team research offers one of the best environments to develop new technologies and refine current ones. This approach applies principles and methods from the quantitative sciences and engineering to address problems in the biological sciences and medicine. A team of scientists from different disciplines may identify problems and develop innovative

solutions more quickly than a researcher working alone. NIH fosters and cultivates cooperative research so that fundamental discoveries and tools can be developed, even when their specific applications might not be obvious. For example, the laser—originally developed in the physics laboratories studying energy and light—has been adapted to invent microscopes that are critical to many research areas as well as a variety of surgical tools, including systems for laser eye surgery. Continued success in the future will require sustained and strong linkages among engineering, clinical medicine, physical science, computational science, and the biological sciences.

Multidisciplinary teams are essential to solving the complex technological problems that many emerging fields present. NIH-supported investigators studying osteoarthritis are working with imaging researchers to develop new ways of diagnosing and assessing the degeneration of cartilage. Using a relatively new imaging technique, optical coherence tomography, along with MRI, the group hopes to create a new method of visualizing the microstructures found in cartilage. (Optical coherence tomography is a technique for obtaining high-quality, three-dimensional, cross-sectional images of tissues using optical beams.) They are but one of several groups recently awarded grants under the Building Interdisciplinary Research Teams (BIRT) program. The initiative promotes interdisciplinary research backed by strong innovation and high potential benefits to advance study in the areas of arthritis and musculoskeletal and skin diseases.

NIH-supported investigators studying osteoarthritis are working with imaging researchers to develop new ways of diagnosing and assessing the degeneration of cartilage.

Building a better mousetrap often means pooling resources and ideas. Partnerships among engineers, clinicians, scientists, and industrial technologists provide a reservoir of information for NIH investigators. One such partnership is creating innovative technologies to assist war veterans who have damaged or lost limbs as well as civilian amputees and those with spinal cord injuries. A range of electronic and robotic devices will help these individuals stand, move, and step. Especially promising is a new generation of hand and arm prostheses that provide fine finger movement and a sense of touch.

Getting to the moon required input from engineers, physicists, computer scientists, bioscientists, and a host of others. Going back into space for a prolonged stay requires the same collaborative effort. NIH recently paired with NASA to support biomedical experiments that astronauts can perform on the International Space Station (ISS). As a national laboratory, the ISS now provides space to researchers from other Federal agencies, universities, and industry. New experiments on the ISS will examine the effects of microgravity and radiation on biological systems. Molecular and cellular biologists and researchers interested in biomaterials and telemedicine are especially needed to design experiments.

Here on Earth, the interplay of ideas among teams of NIH-supported investigators, including clinicians, biomedical researchers, and electrical and computer engineers, has produced promising techniques to identify mothers at risk for premature delivery. One group used a noninvasive ultrasound approach to assess cervical changes in an animal model weeks before the due date. Another group has developed novel computational tools to analyze uterine biomagnetic signals of term and preterm patients to predict the onset of labor. With an early warning of potential preterm delivery, clinicians may have new tools to fight one of the leading causes of infant death in the United States.

Nanotechnology

A sheet of paper is about 100,000 nanometers thick. The field of nanotechnology deals with matter approximately 1 to 100 nanometers in dimension. At these scales, matter exhibits unusual biological, chemical, and physical properties. By bringing together researchers from physics, material science, and engineering, NIH is developing a powerful cadre of investigators who will use nanotechnology to significantly change how we diagnose and treat disease. One such group has used electrical forces generated at the molecular level to suspend a microscopic object in mid-air. This finding could contribute to the design of tiny machines to perform surgery.

Sharing information across disciplines is critical to nanotechnology research. NIH's Alliance for Nanotechnology in Cancer brings together researchers from biology to oncology. The alliance is building a community of cancer nanotechnologists who develop novel approaches to preventing, diagnosing, and treating cancer and sharing that knowledge with the larger medical community. New nanodevices that quickly and accurately assess proteins and DNA structures implicated in cancer, nanoparticle imaging agents to clearly visualize cancer, and implantable nanosensors to monitor cancer progression will reshape the toolkit clinicians use to fight cancer.

NIH's Alliance for Nanotechnology in Cancer brings together researchers from biology to oncology, building a community of cancer nanotechnologists who develop novel approaches to preventing, diagnosing, and treating cancer and sharing that knowledge with the larger medical community.

Oversight for nanotechnology research falls to the Trans-NIH Nanotechnology Task Force, a body established to discover new avenues of study at the nexus of nanotechnology, nanomedicine, and nanobiology as well as to examine the human health effects of engineered nanomaterials. NIH has been named the Government's lead agency for coordination of Federal research on the health implications of nanotechnology under auspices of the National Nanotechnology Initiative's Nanoscale Science, Engineering, and Technology Subcommittee (NSET) and plays a key role in development of its Environmental, Health, and Safety Strategy.

Probing Proteins

Information resulting from the Human Genome Project is now helping scientists as they begin to study proteins, the tiny powerhouses within cells responsible for cell function. By visualizing protein structures, researchers gain a better understanding of many of the biochemical processes related to health and disease. This information also can be used to design drugs that target specific parts of a bacteria, virus, or tumor.

As a result of the NIH-sponsored Protein Structure Initiative (PSI), investigators now have a more potent set of tools to examine the protein in three dimensions. By the end of October 2009, PSI-supported researchers had identified more than 4,000 protein structures. In 2009, NIH announced plans for a new phase of the program—PSI: Biology. During the PSI: Biology phase, highly organized networks of investigators will apply the new paradigm of high-throughput protein structure determination, which was successfully developed during the earlier phases of the PSI, to study a broad range of important biological and biomedical problems. The initiative will make resources for high-throughput structure determination available to a larger community of scientists than has been engaged to date. The majority of targets for structure determination will be defined through consortium partnership arrangements and an open, ongoing community nomination process. Additional targets will be defined through biological theme projects of the structure determination centers.

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Structural biology is a field in which scientists learn about molecules by determining their 3-D structures in atom-by-atom detail. Large user facilities called synchrotrons allow researchers to use X-rays to determine molecular structures more easily, quickly, and cheaply than ever before. NIH funded the development of a new experimental station at the Advanced Photon Source at Argonne National Laboratory. The new station includes three X-ray beamlines for use by scientists from across the United States to determine the detailed, three-dimensional structures of molecules, which will lead to improved understanding of basic biological processes and for drug design.

Transforming Health Care

The combination of new tools and techniques developed to improve basic research as well as those aimed at delivering better health care will transform the current medical paradigm in response to 21st century needs. Health care of the future will include innovations such as neural interfaces to help paralyzed individuals; approaches that will enable diagnostic tests and therapeutic treatment to be administered simultaneously (theranostics); and improvements in the health, quality of life, and productivity of older individuals. NIH-supported researchers are leading the way toward a new paradigm in which technology is a central feature of fast and effective health care delivery. NIH funding of technology development provides an environment that enables investigators to think beyond what is conventional, to do so across disciplines, and to take the health care system to a level that will engage scientists, patients, and physicians in a collaborative experience.

Neural interfaces are systems that operate at the intersection of the nervous system and an internal or external device, including neural prosthetics. Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. NIH pioneered the development of this technology, beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants that help people with hearing impairments, respiratory and hand grasp devices for people with spinal cord injuries, and deep brain stimulation for Parkinson's disease, among other contributions. Current work aims to restore voluntary bowel and bladder control and standing to spinal cord injured persons, allow paralyzed persons to control devices directly from their brains, improve cochlear implants, and improve deep brain stimulation, which may be applicable to many brain disorders. Through the years, this program has fostered the development of a robust research community, now including private sector companies, and represents a cooperative effort between NIH, the Department of Veterans Affairs, and the Department of Defense.

Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. NIH pioneered the development of this technology.

NIH is leading the way in the development of new technologies to provide both disease diagnosis and treatment simultaneously. The concept of combining a therapeutic with a diagnostic agent is rapidly evolving and goes beyond traditional diagnostic tests that screen or confirm the presence of a disease. With specialized molecular imaging techniques and biomarkers, tailored and personalized medicine approaches could predict risks of disease, diagnose disease, and monitor therapeutic response leading to real-time, cost-effective treatment. NIH supports a number of teams that are developing theranostics that can be applied in clinical studies of human patients. A team of chemists and neurosurgeons at the University of Michigan is developing highly specific, dye-loaded nanoparticles capable of delivering targeted photosensitizers to improve the survival of brain tumor patients. These particles also contain imaging contrasting agents to visualize response to therapy. This technique will allow neurosurgeons to visualize the brain tumors for surgical resection of the main tumor mass while eradicating remaining tumor cells through a process known as photodynamic therapy.

A team of chemists and neurosurgeons at the University of Michigan is developing highly specific, dye-loaded nanoparticles capable of delivering targeted photosensitizers to improve the survival of brain tumor patients.

As the baby boomer generation continues to celebrate milestone birthdays, improving the health of older Americans is more important than ever. To that end, NIH supports 13 Edward R. Roybal Centers whose objective is to improve the health, quality of life, and productivity of middle-aged and older people by facilitating translation of basic behavioral and social science to practical outcomes by developing new technologies and stimulating new "use-inspired" basic research in the behavioral and social sciences. Roybal investigators have made several key discoveries. For example, researchers have developed tools and technologies for identifying older adults at risk for automobile crash involvement, and are working with industry partners to develop and disseminate products based on these tools. Additionally, researchers have developed

a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Other companies have used this model to develop related products, and the model has spurred several new grant-funded research projects, including the development of a new medication tracker for older adults.

On many fronts, NIH-supported technology development is making a difference in how we approach both wellness and disease. This knowledge, in turn, will help to improve the quality of life for all.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Diagnostics and Point-of-Care Technology

Point-of-Care Technologies: Testing at the point of initial contact, or point-of-care (POC), rather than at specialized centers or hospitals uses state-of-the-art diagnostics and information systems that can be used in the doctor's office or even at home. Consequently, the use of POC devices also can help patients monitor their wellness in preventive medicine. The POC approach to health care delivery can significantly improve the quality and reduce the cost of health care by: providing earlier diagnosis of disease when treatment is more effective and less costly; making modern medicine available to those who lack access to regular care, such as people in rural settings or developing countries; combining cutting-edge diagnostic and communication technologies to bring patients into more frequent and regular contact with health care providers; and enabling a patient-centered process with home-based monitoring. To address the challenges of health care quality and accessibility, NIH currently funds a network of four Centers that targets the development of new POC technologies for early and rapid detection of strokes, detection of sexually-transmitted diseases, rapid multi-pathogen detection for national disaster readiness, and diagnosis of infections, which can be used in low-resource settings among underserved populations. A major characteristic of the network is to facilitate clinical/technology interactions so that user-specific information can be shared with technology developers who typically lack relevant clinical connections. In 2009, the network funded several collaborative exploratory development projects through clinical need-based solicitations in their respective areas.

→ For more information, see http://www.nibib.nih.gov/Research/POCTRN
→ (E) (**NIBIB**)

Low-Cost, Lens-Free Optical Microscope: The optical microscope is used widely in biological and biomedical research. Since the days of van Leeuwenhoek, the image magnification has been based on lenses. This research explores an innovative design of a lens-free microscope. Images are acquired by direct projection imaging of specimens that flow past the imager in microfluidic channels. Using the innovative design concepts, the microscope device has been fabricated in a package of the size of a dime. Early estimation of the fabrication cost of the optofluidic microscope suggested that such devices can be made very inexpensively at about $10 per unit. This lensless compact microscope can be integrated readily into a point-of-care diagnostic device for applications dealing with rural and global health care

challenges. Large numbers of the compact device can be assembled together for massively parallel imaging of large populations of cells and microorganisms.

→ Cui X, et al. *Proc Natl Acad Sci* 2008;105:10670-5. PMID: 18663227. PMCID: PMC2488383.
→ For more information, see http://www.nibib.nih.gov/HealthEdu/eAdvances/30Apr09
→ (E) (**NIBIB**)

A New Imaging Device for Early Detection of Cataract: A transparent ocular lens is essential to vision. Cataract (clouding of the lens) remains the primary cause of blindness in the world today. Age-related cataract, the most common type of cataract, is caused by abnormal aggregation of lens proteins that clouds the lens. In the last few years, it has been established that a particular lens protein, alpha crystallin, prevents other lens proteins from aggregating and probably plays a major role in preventing cataract formation. Humans are born with a fixed amount of alpha crystallin, so age-related cataracts occur when the supply is depleted. Researchers at NIH and NASA collaborated to develop a new imaging device that allows clinicians to detect and quantify the amount of unbound alpha crystallin protein in a patient's eye. The device uses dynamic light scattering to measure the amount of alpha crystallin remaining in the lens. This may lead to a better understanding of the early stages of protein aggregation before cataracts form that impinge on vision. Early detection of lens protein disruption may provide clues to preventive treatments that could delay the need for cataract surgery.

→ Datiles MB, et al. *Arch Ophthalmol* 2008;126(12):1687-93. PMID: 19064850. PMCID: PMC2600622.
→ For more information, see http://archopht.ama-assn.org/cgi/content/full/126/12/1687
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (I) (**NEI**)

Microchip Captures Early Circulating Cancer Cells: Malignant cancers shed cells that enter the circulation, travel to other areas of the body, and often grow into secondary tumors, or metastases. Indeed, metastases are responsible for the great majority of cancer deaths. It is estimated that 70,000 men per year are diagnosed with recurrent prostate cancer after prostatectomy, as shown by rising prostate surface antigens. For these men, the ability to detect and characterize the malignant cells in the blood may enable personalized therapy. Researchers are developing a technology to facilitate quantitative detection of circulating tumor cells (CTCs). They have engineered a microchip with a large surface area of an adhesion molecule that binds CTCs from whole blood, making detection of CTCs more reliable than previous approaches. They are analyzing molecular and genomic information in the CTCs to identify new biomarkers to customize treatments that are personalized for the patients and to predict treatment outcomes. The NIH-supported research has the potential to eliminate or greatly reduce cancer deaths due to metastases.

→ Nagrath S, et al. *Nature* 2007;450(7173):1235-9. PMID: 18097410.
→ For more information, see http://www.nibib.nih.gov/HealthEdu/eAdvances/31July08
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NIBIB**)

A Test for Taste: Altered taste function has a tremendous impact on food choice, diet, and overall nutritional status. The loss of taste (and smell) impacts the appreciation of food and the desire to eat. This loss exposes an individual to a variety of health risks, including gastrointestinal disorders, heart disease, and diabetes. The true prevalence of taste disorders is not known because scientists lacked a validated taste test that is suitable for large-scale population studies. Such a taste test must be easy to use and can be completed in less than 10 minutes. NIH-supported scientists have adapted a product developed for the food industry (the edible taste strip) to measure human taste capabilities. The precise amount of tastant (sweet, sour, salty, bitter, or savory) can be dissolved in the taste strip, and the strip can be placed in various regions of the mouth (e.g., tongue or palate). The edible taste strip is a sensitive test suitable for the clinic setting to aid the physician

during an examination of an individual who is experiencing problems with their sense of taste. The taste strip can also be used in epidemiological studies for individuals of different ages to establish normative data on the prevalence of taste problems in the general population. This simple, reliable taste test now provides an invaluable diagnostic tool to assess taste function, and, in combination with a smell test, can evaluate chemosensory function.

→ Smutzer G, et al. *Laryngoscope* 2008;118(8):1411-6.
→ (E) (**NIDCD**)

E-Health and Biomedical Information Technology

Multiparameter Intelligent Monitoring in Intensive Care: NIH is funding a team of investigators to develop and evaluate an advanced intensive care unit (ICU) patient monitoring system. The system is designed to substantially improve the efficiency, accuracy, and timeliness of clinical decision-making in intensive care. The investigators are gathering data from ICU medical information systems, hospital medical information systems, and bedside ICU monitors. The project has collected approximately 30,000 patient records for the clinical database as well as ICU monitor data for about 5,000 of these patients for the waveform database. The databases have implemented sophisticated de-identification methods, which they developed, so that the data they collect can be reused by others. For example, they have replaced all dates in the records with surrogate dates. Future work will include the development of innovative algorithms and clinician interfaces based on the need for information extracted from this extensive data set.

→ For more information, see http://mimic.mit.edu/
→ For more information, see http://physionet.mit.edu/physiobank/database/mimic2db/
→ For more information, see http://www.nibib.nih.gov/HealthEdu/eAdvances/31May09
→ (E) (**NIBIB**)

Health Information Technology: Health information technology research that enables the integration of clinical data and medical image diagnostic and treatment data with the patient's medical history in a comprehensive electronic medical record will improve clinical decision-making. The ability to connect and exchange diagnostic information and medical images between health care providers, clinics, and hospitals will help provide the timely information that is needed for effective health care and will help reduce unnecessary, excessive, and duplicative procedures. A patient-centered approach to comprehensive electronic health records will allow patients access to their health information. This will enable patients to play an active role in their own wellness by enabling them to ask knowledgeable questions about treatment options. Additionally, patients also are empowered to provide this information to any and all health care providers as needed, independent of their location or where the medical data was created or stored. NIH supports research in new methods and technologies to address issues such as: interoperability of data systems, compatibility of computer software across medical institutions, security of data during transmission, HIPAA compliance, availability of affordable data systems for patient care providers, and integration of medical decision-support information in medical data systems.

→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E) (**NIBIB**, NLM)

Health IT Standards and Electronic Health Records: NIH researchers are engaged in developing Next Generation electronic health records (EHRs) with advanced decision-support capabilities to facilitate patient-centered care, clinical research, and public health. As the central coordinating body for clinical terminology standards within HHS, NIH works closely with the Office of the National Coordinator for Health Information Technology (ONC) to support nationwide implementation of an interoperable health information technology infrastructure. NIH develops or licenses key clinical terminologies that are designated as standards for U.S. health information exchange. The Unified Medical Language System Metathesaurus, with more than 8.1 million concept names from more than 125 vocabularies, is a distribution

mechanism for standard code sets and vocabularies used in health data systems. NIH also produces RxNorm, a standard clinical drug vocabulary; supports the LOINC nomenclature for laboratory tests and patient observations; and collaborates with the International Health Terminology Standards Development Organisation to promote international adoption of the SNOMED CT clinical terminology. In FY 2009, NIH released the first version of the CORE Problem List Subset of SNOMED CT, designed to facilitate coding of problem list data in EHRs by mapping frequently used terms from seven large-scale health care institutions to corresponding SNOMED CT concepts. The Newborn Screening Codes and Terminology Guide, a Web portal to support more effective use of newborn screening laboratory test information, was created in FY 2009 in collaboration with ONC, the Health Resources and Services Administration, and newborn screening organizations.

→ For more information, see http://www.nlm.nih.gov/research/umls
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**NLM**)

Patient-Reported Outcomes Measurement Information System (PROMIS): The PROMIS initiative is developing new ways to measure patient-reported outcomes (PROs) for clinical research, such as pain, fatigue, physical functioning, emotional distress, and social role participation, which have a major impact on quality of life across a wide variety of chronic diseases. The first phase of PROMIS successfully has addressed its initial broad objectives of developing and testing a large item (survey question) bank for measuring PROs, along with translation of certain items into Spanish; creating a computer adaptive testing (CAT) system that allows for efficient, scientifically robust assessment of PROs in patients with a spectrum of chronic diseases; and producing a publicly available, Web-based system that continues to be updated and modified, to allow clinical researchers access to PROMIS resources, such as a common repository of validated items, a CAT system, and hard copy surveys. Preliminary results demonstrate that a short, 10-item PROMIS survey, administered by CAT, outperforms the most commonly used, paper-based, self-reporting assessment tool for arthritis disability (the Health Assessment Questionnaire). These results are indicative of the anticipated advantages of the PROMIS tool: better answers with fewer patients. The success of the project has garnered 4 more years of NIH funding for PROMIS. Prioritized tasks for PROMIS include validating and evaluating usability in future NIH-supported clinical trials, including Spanish translations; developing additional modes of administration; facilitating adoption of PROMIS by the clinical research community; and building partnerships to secure long-term sustainability for the PROMIS tools.

→ For more information, see http://nihroadmap.nih.gov/clinicalresearch/overview-dynamicoutcomes.asp
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIAMS**, Common Fund - all ICs participate)

Using the Web to Broaden the Delivery of Effective Treatments: NIH is testing the efficacy of delivering evidence-based psychosocial interventions for drug abuse and HIV prevention via the Web or other computer-based media, while assessing their relative cost and efficacy compared to more traditional delivery formats. Variables of interest include abstinence, treatment retention, health risk, quality of life, and social outcomes. New research shows that computer-based training for cognitive behavioral therapy appears to have both short-term and enduring effects on drug use—that is, fewer days of drug use for many months following treatment compared to controls. Another computer-based intervention, called Positive Choice, was tested in HIV-positive patients as a means of reducing risky behaviors that lead to HIV spread. Five San Francisco clinics participated, exposing patients to a "video doctor" to conduct a risk assessment and risk reduction counseling program. Patients waiting to see the provider use a laptop computer to watch video clips and respond by means of a color-coded keyboard. That, too, was successful, and sharply reduced sexual and drug risk behaviors in HIV-positive patients. These delivery methods stand not only to greatly increase cost effectiveness of interventions, but to provide a means for broader dissemination, including to those in remote locations where therapists may not be available. Our research will continue to investigate how such interactive technology can be integrated to improve the addiction treatment system and bring about more widespread adoption of evidence-based approaches.

→ For more information, see http://ajp.psychiatryonline.org/cgi/content/full/165/7/
→ For more information, see http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0001988
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDA**)

A Clearinghouse for Neuroimaging Informatics Tools and Resources: Many neuroimaging tools and databases are underutilized because they cannot be found easily, are not user-friendly, or are not easily adoptable or adaptable. In an effort to promote the enhancement, adoption, distribution, and evolution of neuroimaging informatics tools and resources, the NIH Blueprint for Neuroscience Research has launched the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC). Examples of included tools are: image segmentation, image registration, image processing pipelines, statistical analysis packages, spatial alignment and normalization algorithms, and data format translators. Resources include: well-characterized test datasets, data formats, and ontologies. Since the first release in October 2007, the clearinghouse website, or NITRC, has become host to 180 tools and resources, with a community of 13,602 unique visitors who downloaded NITRC tools and resources, and 7,000 unique visitors per month, more than 954 of which are registered users (11 percent non-English speaking). The hits to the site have reached 15,635,019/month. Since its inception, more than 50,000 software files have been downloaded. More than 53 percent of the tools on NITRC had not been shared online previously but now are available to the community. In 2009, the NITRC project won the first place of Excellence.gov awards, the largest Federal government award program to recognize the very best in government IT programs, among 61 competitors. Through the initiative, nearly 40 awards have been made to neuroimaging tools and resource developers to enhance the accessibility, interoperability, and adoptability of their existing tools and resources.

→ Ardekani BA, Bachman AH. *Neuroimage* 2009;46(3):677-82. PMID: 19264138. PMCID: PMC2674131.
→ For more information, see http://www.nitrc.org/
→ For more information, see http://neuroscienceblueprint.nih.gov/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E) (**NIH Blueprint**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

The Cancer Biomedical Informatics Grid® (caBIG®): The caBIG® initiative connects researchers and institutions to enable collaborative research and personalized, evidence-based care. More than 1,500 individuals representing more than 450 government, academic, advocacy, and commercial organizations have collaborated to develop a standards-based grid infrastructure (caGrid) and a diverse collection of interoperable software tools, enabling basic and clinical researchers to speed the translation of information from bench to bedside. Forty-nine of the 65 NCI-designated Cancer Centers and 8 of 10 organizations of the NCI Community Cancer Centers Program are actively deploying caBIG® tools and infrastructure in support of their research efforts. Additionally, caBIG® technology is adapted to power noncancer research initiatives such as the CardioVascular Research Grid. Ongoing collaborations with research and bioinformation organizations in the United Kingdom, China, and India are driving international adoption of caBIG® resources. The caBIG® infrastructure also supports a new health care ecosystem, BIG Health™, in collaboration with various stakeholders in biomedicine (e.g., government, academia, industry, nonprofits, and consumers) in a novel organizational framework to demonstrate the feasibility and benefits of personalized medicine. BIG Health™ will provide the foundation for a new approach in which clinical care, clinical research, and scientific discovery are linked.

→ For more information, see http://cabig.cancer.gov
→ For more information, see http://bighealthconsortium.org/
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NCI**)

NIH Biowulf Cluster Enables Large-Scale Biomedical Research: The Biowulf cluster provides NIH researchers with a world-class supercomputer that enables the conduct of large-scale biomedical computational projects, allowing scientific research that otherwise would not be possible. Biowulf comprises more than 6,000 interconnected processors operating cooperatively to solve such diverse problems as: identifying genotype patterns of variation across worldwide human populations; validating algorithms used in computer-aided detection of colon polyps ("Virtual Colonoscopy"); computing the molecular structures of viruses such as HIV using 3D electron microscopy; facilitating whole-genome assembly and genome-wide association studies resulting from next-generation DNA-sequencers; and, as part of the NIH Roadmap Initiative for Molecular Libraries, generating conformation ensembles for 25 million chemical structures. In 2008-2009, more than 105 scientific papers published by NIH intramural scientists cited the use of Biowulf as a computational resource.

→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**CIT**)

Informatics Training for Global Health: As biomedical information has increased exponentially in recent years, computer-based tools have been developed to access and analyze this information and to aid the process of research design, data management, and data analysis. The sheer volume of data generated in many biomedical and behavioral research projects and in clinical trials can no longer be managed effectively without electronic help. Further, access to computers and the Internet is becoming commonplace in research institutions throughout the developing world. To take advantage of these tools, individuals with the advanced skills to use them are critically needed. However, despite the central role informatics plays in global health, many low and middle income country (LMIC) institutions have very few informatics experts and a very weak information technology infrastructure. There is a critical need to train local experts who are able to develop local research applications or modify existing platforms to provide tools that are appropriate for the needs, culture, and infrastructure of their institutions and countries. In response, NIH's Informatics Training for Global Health program aims to develop human capital to meet global health challenges, to support the development of research hubs in LMICs, and to bolster the development of expertise in the use of information and communication technologies in support of research and research training.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-09-001.html
→ This example also appears in Chapter 3: *Research Training and Career Development*
→ (E) (**FIC**, NHGRI, NIBIB, NLM)

Children and Clinical Studies: Medical research in children has saved lives and improved health and well-being, yet parents often are reluctant or uncertain about allowing their child to participate in a clinical study. The Children and Clinical Studies campaign helps parents and others to learn more about how clinical research is conducted in children, so that they can make well-informed decisions about whether to participate. Its website, which is available in English and Spanish, combines practical information with award-winning video footage of parents, health care providers, and children themselves discussing the rewards and challenges of participating in research. Educational materials for parents and health care providers can be requested through the site, as well.

→ For more information, see http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php
→ This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
→ (E) (**NHLBI**, NCRR, NICHD)

Gene Sequencing and Beyond

Medical Sequencing: As more is learned about the genetic contributions to disease, DNA sequence information will become even more important for providing medically relevant information to individuals and their health care providers. When it becomes practical to sequence each patient's genome, genetic information will be used to provide more individualized outlooks of disease risk and improve the prevention, diagnosis, and treatment of disease. NHGRI's medical sequencing program, initiated in 2006, aims to drive continued improvement in DNA sequencing technologies and to produce data important to biomedical research. Seven studies are currently underway to identify the genes responsible for several relatively rare disorders and to survey the range of gene variants that contribute to certain common diseases.

→ For more information, see http://www.genome.gov/15014882
→ This example also appears in Chapter 3: *Genomics*
→ (E, I) (**NHGRI**)

Genome Technology and the $100,000 and $1,000 Genome Initiatives: Taking the discoveries made in genetic research initiatives and delivering them to patients on a much wider basis will require significant decreases in the cost and time needed to sequence an entire human genome. Rapid gains have been made on this front since the start of the Human Genome Project and costs continue to fall dramatically. However, it still remains prohibitively expensive to sequence the genomes of individual patients in the clinic. Developing technology to make genome sequencing more affordable is essential for making genomic information part of routine medical care. NIH's Genome Technology program supports research to develop rapid, low-cost methods, technologies, and instruments that will:

- Read DNA sequences
- Check sequences for genetic variations (SNP genotyping)
- Aid research to understand the effects of genetic variations on genomic function.

In 2004, NIH began funding research to develop technologies specifically intended to lower the cost of sequencing the amount of DNA in a human genome, about 3 billion base pairs. These efforts include:

- "Near-Term Development for Genome Sequencing" Grants. These awards support research to enable the sequencing of a human-sized genome for about $100,000.
- Revolutionary Genome Sequencing Technologies Grants. These awards aim to develop breakthrough technologies that will enable an individual's genome to be sequenced for $1,000 or less.

→ For more information, see http://www.genome.gov/10000368
→ For more information, see http://www.genome.gov/27527585
→ This example also appears in Chapter 3: *Genomics*
→ (E) (**NHGRI**)

New Genetics/Epigenetic Tools Shed Light on Addiction: NIH-supported research is taking full advantage of expanding databases and fast technologies to identify links between genetic variations and disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms underlying complex diseases like addiction, which genes strongly influence. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as "gene chips" (e.g., the neurexin gene has been found to play a role in drug addiction). Applying these tools to addiction and other brain disorders advances our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient's genetic profile. To complement these efforts, NIH is investing in the equally important field of epigenetics, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to

epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the deleterious long-term changes to brain circuits from drug abuse. For example, using a powerful new technique known as ChIP-on-chip to monitor epigenetic changes correlated with gene activity, investigators have recently mapped the genomic effects of chronic cocaine use in the reward center of the mouse brain. Such analyses provide needed information about which genes are altered by cocaine and can point to new targets for medications development. Epigenetic discoveries can also inform ways to smartly alter environmental factors so as to decrease the risk for drug abuse and addiction.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-015.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-016.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-09-003.html
→ For more information, see http://nihroadmap.nih.gov/epigenomics/initiatives.asp
→ For more information, see http://nihroadmap.nih.gov/commonfundupdate.asp
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*
→ (E/I) (**NIDA**, NCI, NIAAA, NIMH) (GPRA)

Image-Guided Interventions

Development of Image-Guided Interventions: Image-guided interventions (IGI) provide therapy that can minimize trauma and improve patient outcomes. They are applicable in procedures such as biopsy, surgery, radiation treatment, vascular interventions, and guidance during delivery of devices, drugs, cells, or genes. These improved capabilities particularly are important in light of the shifting trend in medicine toward a model of early, presymptomatic detection of disease. Representative of ongoing research is an effort to improve image-guided surgical removal of tissue using optical coherence tomography (OCT). Recent studies suggest that OCT optical imaging techniques may have a significant impact on breast cancer biopsy and treatment. High-resolution OCT image guidance could help ensure complete surgical removal of tumors and adequate diagnostic biopsy sampling. As other biomedical imaging modalities, such as MRI, improve the ability to detect small suspicious lesions, OCT can be used to guide a biopsy needle precisely to tumor tissue and cells and enable sampling of these smaller nonpalpable lesions. In preliminary studies, surgically removed lumpectomy specimens from more than 65 patients have been imaged with OCT in the operating room. When compared to post-operative histopathology, OCT yielded a sensitivity of 100 percent and a specificity of 82 percent and demonstrates the potential of OCT as a real-time method for the intraoperative margin assessment in breast-conserving surgeries.

→ Nguyen FT, et al. Meeting Abstract: Optical coherence tomography (OCT) as a diagnostic tool for the real-time intraoperative assessment of breast cancer surgical margins. *Cancer Res* 2009;69: 802.
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NIBIB**) (GPRA)

Image-Guided, Minimally Invasive Interventions: Image guidance offers a cost-effective, safe, and less invasive approach to many common diseases. From treating a uterine fibroid, a brain aneurysm, or cancer, image-guided minimally invasive interventions are ushering in an era of personalized and cost-effective alternatives to open surgery. Diagnosis and therapy often are poorly integrated, creating a gap in health care delivery. NIH support of technology development has enabled physicians to better use medical imaging during minimally invasive procedures, not solely for pre- or post-procedure diagnosis. The unique translational environment of the NIH CC has enabled interdisciplinary and trans-agency development and dissemination of novel cost-effective approaches. This includes navigation with "Medical GPS" for tumor ablation, whereby a "smart" needle is inserted with image guidance into a tumor to heat and kill cancer cells. The heat also deploys nanoparticles at the site of the tumors that are engineered specially to deploy their chemotherapy cargo where needed to avoid systemic toxicities. Such drug + device + imaging combination therapies were pioneered by NIH as part of an inter-agency, multi-IC, and industry-academic partnership. Using prior images during later invasive procedures

makes the procedures targeted and personalized, without requiring the expensive imaging equipment to be brought physically to the procedure room. Imaging also has been used to guide energy (high-intensity focused ultrasound) through the skin, to the level of the inner disease process to kill tissue or to deposit drugs in a targeted fashion.

→ For more information, see http://www.cc.nih.gov/centerio/index.html
→ For more information, see http://www.cc.nih.gov/drd/irlab/index.html
→ For more information, see http://www.cancer.gov/ncicancerbulletin/061609/page4
→ (I) (**CC**, NCI, NHLBI, NIBIB)

Imaging Biological Systems

High Resolution Anatomical and Functional Imaging of the Human Brain: NINDS and NIMH Intramural Research Programs are partnering to push the frontiers of MRI (magnetic resonance imaging) of the human brain and to make these developments available to researchers. The NINDS Laboratory of Functional and Molecular Imaging has led development of the next generation MRI device that uses a powerful 7T (Tesla) magnet, compared to the usual 1.5T magnetic strength. Overcoming the many technical challenges of imaging at 7T has yielded extraordinarily detailed images, which have contrast and spatial resolution as much as 100 times better than previous methods. These images reveal structures never before seen in the living human brain that may be critical in detecting early stages of disease. The NIMH functional MRI core facility serves more than 30 principal investigators on the NIH Bethesda campus and leads development of functional brain imaging. The facility has played a major role in making 3T MRI widely available for routine use. Together NINDS and NIMH investigators have pioneered imaging methods that increase the detail of structural and functional changes that investigators can detect in the brain, while improving time resolution and shortening duration for brain scans. A two-step strategy to continue this successful program will first translate 7T MRI from its present prototype design to routine use and then develop one of the world's first 11.7T MRI devices for imaging the human brain. Increased MRI resolution will improve diagnosis and monitoring of neurological and psychiatric disorders and open new opportunities for understanding brain function.

→ For more information, see http://intramural.nimh.nih.gov/fmri/fmri_research.html
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
→ (I) (**NINDS**, NIMH)

Feeling Organs with Imaging: MRI is known for providing exquisite anatomical images of internal organs. Using a new technique that involves imaging while pushing on an organ with sound waves, researchers are able to feel the stiffness of internal organs. Because tumors often are more stiff than normal tissue (think, for example, of feeling for a "lump" of stiffer tissue in the breast), this technique may provide important diagnostic information about disease. Initially, this technique is being used to examine the stiffness of liver and potentially provide an alternative to liver biopsy for the 170 million individuals worldwide who live with chronic hepatitis C, a major cause of liver disease.

→ Venkatesh SK, et al. *AJR Am J Roentgenol* 2008;190:1534-40. PMID: 18492904.
Yin M, et al. *Magn Reson Med* 2007;58:346-53. PMID: 17654577.
Yin M, et al. *Clin Gastroenterol Hepatol* 2007;5:1207-13. PMID: 17916548. PMCID: PMC2276978.
Kruse SA, et al. *Neuroimage* 2008;39:231-7. PMID: 17913514. PMCID: PMC2387120.
→ For more information, see http://www.nibib.nih.gov/HealthEdu/eAdvances/28Aug08
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIBIB**)

NCI Imaging Programs: In addition to their applications in basic scientific discovery, imaging technologies contribute to cancer care through contributions to screening, diagnosis, disease staging, treatment guidance, treatment monitoring, and detection of cancer recurrence. NCI's imaging programs include the extramural Cancer Imaging Program (CIP), whose mission is to promote and support basic, translational, and clinical research in imaging sciences, and several intramural efforts within the Center for Cancer Research (CCR), such as the Molecular Imaging Program, Radiation Biology Branch, Radiation Oncology Branch, Center for Interventional Oncology, and NCI-Frederick Small Animal Imaging Program. The National Lung Screening Trial (NLST) is comparing two ways of detecting lung cancer: spiral computed tomography (CT) and standard chest X-ray. Both chest X-rays and spiral CT scans have been used to find lung cancer early. So far, neither chest X-rays nor spiral CT scans has been shown to reduce a person's chance of dying from lung cancer. This study will aim to show if either test is better at reducing deaths from this disease.

→ For more information, see http://imaging.cancer.gov
→ For more information, see http://home.ccr.cancer.gov/connections/features2.asp
→ For more information, see http://www.cc.nih.gov/centerio/index.html
→ For more information, see http://web.ncifcrf.gov/rtp/lasp/intra/saip/
→ For more information, see http://www.cancer.gov/NLST
→ This example also appears in Chapter 2: *Cancer*
→ (E/I) (**NCI**) (GPRA)

Simulating and Analyzing Musculoskeletal Dynamics: NIH-funded investigators have introduced OpenSim, a freely available open-source simulation platform to accelerate the development and sharing of simulation technology and to integrate dynamic simulations into the field of movement science, in particular animal and human neuromusculoskeletal systems. OpenSim tools allow one to edit muscles, analyze dynamic simulations, and track motions, a process that enables accurate muscle-driven simulations to be generated that represent the dynamics of individual subjects. OpenSim is being developed and maintained on Simtk.org, which is a software development environment that is being developed under the parent Roadmap Simbios National Center for Biomedical Computing.

→ Liu MQ, et al. *J Biomech* 2008;41(15):3243-52. PMID: 18822415.
→ (E) (**NIGMS**)

Molecular Imaging Probe Development Program Review: An emerging biomedical technology with great potential for improving disease diagnosis and treatment is molecular imaging. However, molecular imaging techniques still are used primarily for preclinical applications. The transfer of these preclinical tools into clinical tools remains a demanding problem and requires the development of novel molecular imaging probes that have increased sensitivity and specificity, and are nontoxic. Approaches to developing more sensitive and specific nontoxic probes were discussed and developed at a Molecular Imaging Program Progress Review that was held on May 19, 2008, in Bethesda, MD. The panel identified high-priority areas that would advance future research in the molecular imaging field, and, in particular, would be capable of translation to clinical applications. The report of this panel discussion was posted on the NIBIB website and provided to the National Advisory Council for Biomedical Imaging and Bioengineering for further strategic planning in this area.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-09-016.html
→ (O) (**NIBIB**)

Investments in Infrastructure

Shared Instrumentation Grant and High-End Instrumentation Programs: The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained

through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the $100,000-$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the $750,000-$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located at core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2008, the SIG program funded a total of 82 grants for $30,623,406; the HEI funded a total of 20 awards for $33,309,434. In FY 2009, NIH received $300 million in ARRA funding to provide shared instrumentation to extramural researchers through the SIG and HEI programs. To best serve the needs of NIH-supported investigators, the range of HEI awards funded by ARRA was expanded and now is $600,000 to $8 million.

→ For more information, see http://www.ncrr.nih.gov/btinstruments
→ For more information, see http://www.ncrr.nih.gov/recovery
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**) (ARRA)

Extramural Construction Program Expands Research Capacity: The American Recovery and Reinvestment Act (ARRA) provided $1 billion to NIH for the Extramural Construction program. The program will build capacity to conduct biomedical and behavioral research by supporting the costs of improving non-Federal basic research, clinical research, and animal facilities to meet the research, research training, or research support needs of institutions. One component of the program, the Extramural Research Improvement Program, awards grants to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities for biomedical and behavioral research. Another component of the program, the Core Facility Renovation, Repair, and Improvement activity, awards grants to public and nonprofit private entities to renovate, repair, or improve core facilities. A core facility is a centralized shared resource that provides access to instruments or technologies or services, as well as expert consultation to investigators supported by the core. Institutions apply for construction grants by submitting applications, which are selected using NIH's standard, competitive, peer-reviewed process. Funding decisions are based on the scientific and technical merit of the application as determined by first and second level of peer review, the availability of funds, the relevance of the application to NIH program priorities, the national geographic distribution of awards, and the priorities specified in the ARRA, such as energy efficiency and job creation. The objective of the ARRA Extramural Construction program aligns with the objective of the existing Research Facilities Improvement Program, which is also administered by NIH.

→ For more information, see http://www.ncrr.nih.gov/recovery/construction
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**) (ARRA)

ARRA-Funding Expands Research Capabilities: NCRR is using its ARRA funds designated for scientific research to accelerate the Center's research priorities and support research, resources, tools, and training to help researchers funded by NIH transform basic discoveries into improved human health. In contrast to most of the NIH ICs that fund primarily Research Project Grants (i.e., R01s), NCRR primarily supports large Center programs that build research capacity and offer training and career development. Consistent with NCRR's research portfolio, a few previously reviewed Research Project Grants (R01s and R21s) are being awarded with ARRA funds. Through competitive revision awards, NCRR is encouraging NIH-funded researchers (primarily supported by other NIH ICs) to leverage the resources, expertise, and infrastructure of NCRR centers and Center-like programs. To further advance the scientific progress of NCRR programs, administrative supplements are being awarded to: advance translational (pre- and post-clinical) research, achieve CTSA

consortium strategic goals, enhance NCRR pilot project mechanisms, promote collaborative community engagement research, improve research workforce development, and strengthen science education and dissemination. A new ARRA-supported initiative will develop infrastructure to connect people and resources across the Nation and promote interdisciplinary collaborations and scientific exchange. Additional ARRA funding is supporting NIH-led activities such as the Challenge Grants and the Summer Research Experiences for Students and Science Educators. From the beginning of the ARRA-funding strategy development, NCRR leadership decided to align its ARRA activities broadly with the goals and objectives of the NCRR 2009-2013 Strategic Plan.

→ For more information, see http://www.ncrr.nih.gov/recovery
→ For more information, see http://www.ncrr.nih.gov/strategic_plan/implementation/
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**) (ARRA)

Electronic Scientific Portfolio Assistant: Demand for information about program performance and results, as well as accountability and transparency, continues to increase across the Federal government. The Electronic Scientific Portfolio Assistant (e-SPA) offers a comprehensive means by which to conduct statistically meaningful portfolio analyses of program performance. The development of e-SPA grew out of program needs to ensure accountability and transparency of information about program performance and results. Though e-SPA was developed initially for NIAID program managers, it quickly has become a valuable analysis tool across NIH. e-SPA provides extramural program directors with the capability to monitor, analyze, and compare the performance of their research portfolios and individual investigators. The tool generates user-defined portfolios of research projects and links the projects to outcome indicators including funding, publications, citations, impact factors, inventions, and patents. e-SPA uses information available from multiple databases to enhance synthesis and analysis of relevant data, and provides data visualization capability through a dashboard and graphs.

→ (O) (**NIAID**)

Insights from Animal Models

New Biomaterials System Programs Cells in situ to Fight Cancer: In the body's immune response to foreign invaders, dendritic cells signal and activate other cells to initiate a generalized inflammatory response. Cell-based cancer vaccinations build on this natural tendency by isolating and activating a patient's dendritic cells using tumor antigens, and then injecting the reprogrammed cells back into the patient. The activated dendritic cells travel home to the lymph nodes and promote an antitumor response. Unfortunately, most transplanted dendritic cells die. Additionally, reprogrammed cells partially lose their effectiveness after injection back into the body. Thus, multiple rounds of injections are required to achieve significant effect. To address these limitations, investigators developed a multifunctional in situ dendritic cell reprogramming system composed of polymeric biomaterials that release cytokines to attract dendritic cells already within the lymph nodes into the biomaterials. The dendritic cells are then activated by the biomaterials. The biomaterials reduce their cytokine release at a controlled rate so that after activation, the dendritic cells will migrate away from the biomaterials back home to the lymph nodes and present tumor antigens to T cells found there. In a mouse model this sophisticated system provided protection from tumor development equal or superior to that provided by traditional cancer vaccines without the complications and costs of ex vivo cell manipulation and transplantation. The new system also provided much better control over the number of dendritic cells than traditionally generated cancer vaccines. This study demonstrates a powerful new application for polymeric biomaterials that could be used in the future against cancers and other diseases.

→ Ali OA, et al. *Nature Materials* 2009;8(2):151-8. PMID: 19136947. PMCID: PMC2684978.
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NIDCR**)

New Model Reveals Novel Molecular Strategies in the Fight to Overcome Oral Cancer: Oral and pharyngeal carcinomas are the ninth most common cancer worldwide, with more than 35,000 new patients and more than 7,500 deaths each year in the United States alone. The 5-year survival rate has improved only marginally over the past 40 years. There is an urgent need for new options for these patients. Emerging information on the deregulation of normal molecular mechanisms that result in the cancer's progression provides the possibility of new mechanisms-based therapeutic approaches for these aggressive oral malignancies. NIH scientists recently used a two-step chemical carcinogenesis model and found that the drug rapamycin exerted a remarkable anticancer activity. It decreased the tumor burden of mice having early and advanced tumors, and even brought about the regression of recurrent squamous cell skin cancers. The scientists reported that the persistent activation of mTOR, the mammalian Target of Rapamycin, occurs frequently in head and neck cancer patients and that its inhibition by rapamycin causes regression of human oral cancer tumors implanted in mice. Because chemically induced animal cancer models often better reflect the complexity of the clinical setting, the scientists developed an oral-specific chemical carcinogenesis mouse model. In this model, activation of mTOR is an early event in precancerous lesions; rapamycin treatment can halt the malignant conversion of precancerous lesions and promote the regression of advanced carcinogen-induced oral squamous cell carcinomas (SSCs). Significance: The development of this SCC carcinogenesis model demonstrates that the use of mTOR inhibitors may provide a novel molecular-targeted strategy for chemoprevention and treatment of oral squamous cell cancer.

→ Amornphimoltham A, et al. *Clin Cancer Res* 2008;14(24):8094-101. PMID: 19073969.
Czerninski R, et al. *Cancer Prevention Res* 2009;2(1):27-36. PMID: 19139015.
→ For more information, see http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/OralCancer/
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Research*
→ (I) (**NIDCR**)

Bone Marrow Stromal Cells Help Fight Sepsis: Sepsis is a serious medical condition that affects 18 million people per year worldwide, and is characterized by a generalized inflammatory state caused by bacterial infection. Widespread activation of inflammation and blood clotting pathways leads to multiple organ failure, collapse of the circulatory system (septic shock), and death. In the last few years, it has been discovered that bone marrow stromal cells (BMSCs, also known as mesenchymal stem cells) are potent modulators of immune responses. In this study, BMSCs were administered before or shortly after inducing sepsis by puncturing the intestine to determine whether BMSCs injected into the circulation would have a beneficial effect in preventing or attenuating septic shock. Infusion of BMSCs significantly decreased sepsis-induced mortality and increased organ function in an animal model. The effects appear to be mediated by the production of Prostaglandin E2 when BMSCs are activated during the early stages of sepsis. Prostaglandin E2 subsequently induces the recipient's macrophages to produce substantially more IL-10, a factor that dampens the inflammatory response, which if left unabated, leads to death. This is the first determination of a mechanism by which BMSCs modulate the immune response in an animal model of sepsis. As many people die of sepsis annually as die from heart attacks. A new treatment or preventative regimen desperately is needed. Since the animal model suggests that the BMSCs need not be isolated from the same individual as will receive them, it is possible that cells isolated from nonrelated donors could be prepared and stored for use in patients with high risk for sepsis.

→ Nemeth K, et al. *Nat Med* 2009;15(1):42-9, PMID: 19098906. PMCID: PMC2706487.
→ For more information, see http://www.nature.com/nm/journal/v15/n1/abs/nm.1905.html
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Molecular Biology and Basic Research*
→ (I) (**NIDCR**)

Bioactive Nanostructures for Neural Regeneration: Spinal cord injury (SCI) often leads to permanent paralysis and loss of sensation below the site of injury because of the inability of damaged axons to regrow across the injury site in adults. Nanomaterials built from a family of self-assembling molecules may offer hope for treating serious injuries, such as spinal cord injury according to new results from NIH research. Recently, an NIH-supported research group developed peptide amphiphile (PA) molecules that self-assemble in vivo into supramolecular nanofibers and tested them on mouse models of spinal cord injury. In this work, in vivo treatment with the PA nanofibers, after SCI, reduced cell death and promoted regeneration of both motor fibers and sensory fibers through the lesion site. Treatment with the PA also resulted in significant behavioral improvement. These observations demonstrate that it is possible to inhibit glial scar formation and to facilitate regeneration after SCI using bioactive three-dimensional nanostructures displaying high densities of neuroactive epitopes on their surfaces.

→ Tysseling-Mattiace VM, et al. *J Neurosci* 2008;28(14):3814-23. PMID: 18385339. PMCID: PMC2752951.
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIBIB**)

Using Mice to Examine Hearing and Balance Disorders: Mouse models of hereditary hearing impairment have been instrumental in mapping and cloning many deafness genes in humans. These animal models offer researchers many opportunities to study deafness, hereditary factors involved in hearing loss, and genes that are critical for the development and maintenance of the human ear. For example, the varitint-waddler mouse exhibits hearing loss due to a mutation in the Trpml3 gene that encodes the protein, TRPML3, which is responsible for mechanosensory conduction within the inner ear. Mutations in the Trpml3 gene cause disorganization of the stereocilia bundle of sensory hair cells in the inner ear, which ultimately leads to hearing loss. The senses of hearing and balance are highly dependent on the structure of the stereocilia bundles. In this study, NIH intramural scientists, in collaboration with scientists in the United Kingdom, used immunofluorescence to locate the Trpml3 protein in the base of developing and growing auditory hair cell stereocilia. This study identifies Trpml3 as a critical channel in maintaining the base of the bundle during stereocilia maturation, which appears to be necessary to establish a functioning stereociliary hair bundle. Mouse models of hearing impairment are important tools to unravel the molecular basis of hearing. They also, in many instances, faithfully mimic the pathophysiology and genetics of human hearing impairment, thus providing animal models to explore the mechanism of action.

→ van Anken AF, et al. *J Physiol* 2008;586(Pt 22):5403-18. PMID: 18801844. PMCID: PMC2655368.
→ (I) (**NIDCD**)

Researchers Discover Why Mammalian Teeth Form in a Single Row: Why do mammals develop a single row of teeth whereas other vertebrates, such as sharks, can develop multiple rows of teeth? Researchers studying mutations in the genes of mice that develop teeth serving no apparent function may have solved the mystery. Most of the mutations under study caused the mice to develop the extra teeth within the space between the normal incisor and the normal first molar. Since tooth buds normally develop within this part of the developmental field but later regress, these genetic alterations did not alter the normal plane within which teeth developed. However, one particular mutation had a different result. The researchers found that a knockout mutation (i.e., elimination) of a gene known as Odd-skipped related 2 (Osr2) also resulted in the production of extra teeth, but strikingly, these teeth developed outside the usual plane, on the tongue side of the normal molars, suggesting that the mutation results in an expansion of this developmental field in the affected mice. Supporting this theory, the knockout mice (i.e., mice lacking Osr2) have spatially expanded expression of other genes involved in tooth development. That suggests that normal Osr2 acts to restrict tooth development to within its usual, single-row plane. Previous work from this group discovered the Osr2 gene and demonstrated that it is a novel regulator of palate formation. The current study demonstrates that Osr2 function also is critical to the patterning of tooth formation and

sheds light on the restriction of teeth to a single row in mammals. Osr2 function may be an important consideration for researchers seeking to grow replacements eventually for lost teeth in adults.

→ Zhang Z, et al. *Science* 2009;323:1232-4. PMID: 19251632. PMCID: PMC2650836.
→ For more information, see http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/CurrentSNIB/March/SingleRow.htm
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDCR**)

Large-Scale Collaborative Activities

Biomedical Technology Research Centers (BTRCs): The BTRCs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Centers and through intensive collaborations with other leading laboratories. The BTRCs are used annually by nearly 5,000 scientists from across the United States and beyond, representing more than $700 million of NIH funding from 22 ICs. As an example, optical technologies enable researchers to:

- Harness the power of light to "see" biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

→ For more information, see http://www.ncrr.nih.gov/biomedical_technology
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**)

Biomedical Informatics Research Network (BIRN): Modern biomedical research generates vast amounts of diverse and complex data. Increasingly, these data are acquired in digital form, allowing sophisticated and powerful computational and informatics tools to help scientists organize, store, query, mine, analyze, view, and, in general, make better use and sense of their data. Moreover, the digital form of these data and tools makes it possible for them to be shared easily and widely across the research community at large. NIH has supported development of the BIRN infrastructure to share data and tools by federating new software tools or using the infrastructure to federate significant datasets. BIRN fosters large-scale collaborations by using the capabilities of the emerging national cyberinfrastructure. In FY 2009, the BIRN Coordinating Center transitioned to a new home at the University of Southern California. The new BIRN Coordinating Center uses grid computing technology to create a virtual organization for basic and clinical science investigators across the network. In addition, a new BIRN Community Service (U24) grant was awarded to help expand the BIRN user community to researchers and clinicians beyond the neuroscience and imaging fields.

→ For more information, see http://www.ncrr.nih.gov/birn
→ For more information, see http://www.nbirn.net
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E) (**NCRR**)

Center for Human Immunology, Autoimmunity, and Inflammation: The Center for Human Immunology, Autoimmunity, and Inflammation (CHI) is a new trans-NIH intramural initiative designed to study the human immune system. Integrated teams of physicians and basic scientists are organized by CHI to perform research into immune pathophysiologies, the role of inflammation in a wide variety of disorders, and the translation of new knowledge into improvements in diagnosis and treatment of disease. The Center provides unique specific technologies often unavailable to individual laboratories because of cost, complexity, and novelty. The core of CHI is made up of three technology centers. The first center features assays of immune cells and their products, based mainly on a technique known as flow cytometry and similar emerging techniques. The second center contains high-throughput systems technologies, involving the use of new methods for large-scale examination of genes, proteins, enzymes, and/or lipids. It also features advanced biostatical and computer modeling methods for mining these diverse data sets, thereby providing for a deeper understanding of immune function and pathology. The third center is based in protocol development, with staff dedicated to producing methods that efficiently translate to the clinic while considering all of the ethical and regulatory requirements for human research.

→ For more information, see http://www.nhlbi.nih.gov/resources/chi/index.htm
→ This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*
→ (I) (**NIAMS**, NCI, NHLBI, NIAID, NICHD, NIDDK, NINDS)

Analytical Methods and Reference Materials (AMRM) Program: The rapid expansion of the dietary supplement marketplace has resulted in a proliferation of ingredients and products and overtaken the pace of development of reliable analytical methods. Precise, accurate, and rugged analytical methods and reference materials are essential for verification of ingredient identity and measuring the amounts of declared ingredients in raw materials and finished products. Also, dietary supplement labels are required to list certain facts about product identity and content and to be truthful and not misleading. That this is not always the case is due in part to the lack of proven and agreed-upon methods to precisely assess the quantity of constituents of many supplements and supplement ingredients. NIH's congressionally mandated AMRM program is intended to assist in providing these critical tools for quality assurance. The program promotes development, validation, and dissemination of analytical methods and reference materials for commonly used dietary supplement ingredients. Responding to concerns about the quality and accuracy of standards and methods used by testing laboratories to measure vitamin D in the body, NIH, in collaboration with the National Institute of Standards and Technology, has developed a new Standard Reference Material (SRM) for vitamin D in blood serum to help laboratories evaluate their analytical methods. This SRM represents a first step toward standardization of vitamin D testing.

→ For more information, see http://dietary-supplements.info.nih.gov/Research/Analytical_Methods_and_Reference_Materials_Program.aspx
→ (E) (**ODP/ODS**, ORWH)

National Centers for Biomedical Computing: There are seven NIH Roadmap National Centers for Biomedical Computing (NCBC). Funded as cooperative agreements, these centers collectively cover broad areas of neuroinformatics, functional genomics, image post processing, multiscale modeling, cellular pathways, semantic data integration and ontologies, information networks, cellular networks and pathways, clinical informatics, disease-gene-environment analysis, and clinical decisions support.

→ For more information, see http://ncbcs.org/
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E) (**NIGMS**, Common Fund - all ICs participate)

Glycomics Technology Development, Basic Research, and Translation into the Clinic: Glycans are ubiquitous complex carbohydrates found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules is thus critical for basic and clinical research across the spectrum of health and disease, but widely is regarded as one of the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- Biomedical Technology Research Centers develop and share cutting-edge technologies for analysis of carbohydrates in complex biological systems.
- Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.
- Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
- A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.

→ For more information, see http://www.ncrr.nih.gov/glycomics
→ For more information, see http://www.functionalglycomics.org
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**, NCI, NHLBI, NIGMS, NINDS)

Multidisciplinary and Interdisciplinary Research

Building Interdisciplinary Research Teams (BIRT) Awards: The scale and complexity of biomedical research demands that scientists move beyond the confines of their individual disciplines and explore new organizational models for team science. Integrating different disciplines holds the promise of opening scientific avenues of inquiry and, in the process, potentially forms new disciplines for addressing increasingly complex questions. The BIRT award was created by NIH to promote interdisciplinary research by supplementing collaborations with high innovation and potentially high impact in general areas of arthritis, musculoskeletal, and skin biology and diseases. In 2008, 11 grants were awarded for the following areas of collaboration: developmental biology—systems biology, soft tissue biology—imaging technologies, tissue engineering—immunology, and tissue engineering—developmental biology.

→ For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2008/birt.asp
→ For more information, see http://www.niams.nih.gov/Funding/Funding_Opportunities/Supported_Scientific_Areas/Musculoskeletal_Diseases/birt_faq.asp
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-08-001.html
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIAMS**)

Prostheses to Restore Lost Function: Many veterans return home with significant injuries to their extremities, including loss of limbs. Through multidisciplinary partnerships between engineers, clinicians, scientists, and industrial partners, NIH investigators are developing new and novel technology for assistive rehabilitation, such as electrodes for neural and muscular recordings, networked implantable systems for functional electrical stimulation, robotics for rehabilitation, and brain computer interface systems for communication and control. For example, next-generation hand and arm prosthesis systems controlled by intact muscle recordings will be able to produce fine finger movements and provide to the user the

sensation of position and force applied to an artificial hand. Other examples include multifunctional stimulation systems that allow spinal cord-injured subjects to change posture, stand, step, and control hand and arm function.

→ Weir RF, et al. *IEEE Trans Biomed Eng* 2009;56(1):159-71. PMID: 19224729.
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NIBIB**)

Stem Cells and Regenerative Medicine: Stem cells are able to renew themselves and generate progeny that differentiate into more specialized cells. They play critical roles in organism development, and some are essential for normal homeostasis and tissue repair. NIH has made a significant investment in stem cell research. One NIH-supported study showed that the sex of cells in a subpopulation of muscle-generating stem cells in adult mice can influence their capacity to repair tissue considerably. This finding could lead to future therapies for various diseases, including muscular dystrophy. A collaboration between NIH Intramural researchers and those at Walter Reed Army Medical Center discovered that waste tissues from surgery, removed to promote healing of orthopaedic injuries and war-traumatized muscle, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells. They could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest cells. NIH has partnered with the Department of Defense on an initiative to speed treatments to wounded soldiers abroad, and civilian trauma victims and burn patients in the United States. This collaboration has resulted in the establishment of the new Armed Forces Institute of Regenerative Medicine (AFIRM). The AFIRM-led program will focus on regrowing fingers, repairing shattered bones, and restoring skin to burn victims with genetically matched skin, to pave the way for commercial products in the near future. Hair follicles are useful models for organ regeneration. Recent discoveries have been made in the molecular processes that govern the growth of hair follicle stem cells, which are a source for newly formed hair follicles.

→ Deasy BM, et al. *J Cell Biol* 2007 Apr 9;177(1):73-86. PMID: 17420291. PMCID: PMC2064113.
Jackson WM, et al. *J Tissue Eng Regen Med* 2009 Feb;3(2):129-38. PMID: 19170141.
Plikus MV, et al. *Nature* PMID: 18202659. PMCID: PMC2696201.
Horsley V, et al. *Cell* 2008 Jan 25;132(2):299-310. PMID: 18243104. PMCID: PMC2546702.
Nesti LJ, et al. *J Bone Joint Surg Am* 2008;90(11):2390-8. PMID: 18978407. PMCID: PMC2657299.
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cell_sex_and_stem_cell.asp
→ For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/progenitor_cells.asp
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NIAMS**, NIA, NIAID, NIBIB)

Cooperation in Space-Related Health Research: In FY 2009, NIH and the National Aeronautics and Space Administration (NASA) issued a funding opportunity announcement to support biomedical experiments that astronauts could perform on the International Space Station (ISS). The ISS provides a special microgravity and radiological environment that Earth-based laboratories cannot replicate. Congress, recognizing the immense promise the facility holds for American-led science and technology efforts, opened the U.S. portion of the ISS to other Federal agencies and university and private sector researchers when it designated the U.S. resources as a National Laboratory in 2005. Recently published ISS experiments from investigators supported by NIH and NASA have offered new insights into how bacteria cause infectious disease. The FY 2009 solicitation is the next step in a partnership to apply the National Laboratory to research that complements NASA's space exploration efforts. The program encourages a new cadre of health researchers from a variety of disciplines to incorporate the space environment into their experiments, and will support them as they prepare their experiments for launch and analyze their data following a mission. Applications particularly are encouraged

from researchers who are interested in molecular or cellular biology, biomaterials, or telemedicine. NIH expects to fund applications in FY 2010, FY 2011, and FY 2012, and to send experiments into space by 2011.

→ Wilson JW, et al. *Proc Natl Acad Sci U S A* 2007;104(41):16299-304. PMID: 17901201. PMCID: PMC2042201.
→ For more information, see http://www.niams.nih.gov/News_and_Events/NIH_NASA_Activities/default.asp
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIAMS**, NCI, NCRR, NHLBI, NIA, NIAAA, NIBIB, NICHD, NINDS)

Researchers Developing a Noninvasive Ultrasound Technique to Detect Early Signs of Premature Delivery: Premature delivery is one of the leading causes of infant mortality in the United States, according to CDC. Currently, clinicians only can attempt to delay delivery once the extensive uterine contractions of labor have been initiated in the final stages of the delivery process. However, because the cervix prepares for delivery weeks to months before labor in a process termed "preterm cervical ripening," an NIH-supported scientist, together with a team of electrical and computer engineers, theorized that a noninvasive ultrasound technique might be used to detect this early warning sign well in advance of premature delivery. The research team developed and tested such a technique using computer simulations in rat tissue samples, followed by studies with live rats. The results were promising in that cervical changes clearly were identifiable using this technique in the tissue samples. With further development, this innovative technique could prove powerful in identifying mothers at risk for premature delivery, thereby reducing or preventing the associated morbidity and mortality.

→ Bigelow TA, et al. *J Acoust Soc Am* 2008;123(3):1794-800. PMID: 18345867. PMCID: PMC2637349.
→ For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18345867
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NINR**)

Facilitating Interdisciplinary Research via Innovation in the Behavioral and Social Sciences: An NIH Roadmap Funding Opportunity Announcement (FOA), Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences, was released. Using a modified Exploratory/Developmental (R21) mechanism, this FOA solicits applications to develop new and innovative measures, methods, and technologies that support the integration of human social and/or behavioral science with other disciplines across varying levels of analysis. Supported projects have included: creation of tools to measure sun exposure and vitamin D, models of spinal cord injury, and an Internet-based system for providing feedback to teachers and consultants on the school readiness and mental health of children. Several national conferences have been planned in relation to this initiative, including *Facilitating Interdisciplinary Research: Methodological and Technological Innovation in the Behavioral and Social Sciences* (October 2009).

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-004.html
→ For more information, see http://nih.blhtech.com/roadmap09/
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDA, OBSSR**, Common Fund - all ICs participate)

Interdisciplinary Research Consortia Funded by the NIH Roadmap: One of the four main initiatives established by the NIH Roadmap's Interdisciplinary Research Work Group was a grant program to fund large-scale consortia to support interdisciplinary research. In total, NIH funded nine collaborative teams located across the United States. Each focuses on a particular health problem or process, including substance abuse and stress; obesity; developmental disorders; the process of aging; providing fertility options for cancer survivors; engineering healthy tissue to treat diabetes, heart disease and oral/craniofacial disorders; psychiatric disorders; drug/medications development; and genome engineering. The initial

results suggest ways in which this team science approach helps to increase cooperation within and between academic institutions, as well as advancing the individual missions of NIH ICs.

→ For more information, see http://nihroadmap.nih.gov/interdisciplinary/
→ For more information, see http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp
→ For more information, see http://nihroadmap.nih.gov/interdisciplinary/members.asp
→ For more information, see http://nihroadmap.nih.gov/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E, O) (**NIDCR**)

Exposure Biology Program: The Genes, Environment, and Health Initiative (GEI) aims to accelerate the understanding of genetic and environmental contributions to health and disease. It has two components: the genetic component that focuses on identifying major genetic susceptibility factors, and the environmental component that focuses on development of innovative techniques to measure environmental exposures, diet, physical activity, psychosocial stress, and addictive substances that may contribute to development of disease. This program addresses the second effort, the Exposure Biology Program (EBP), which will create new ways to assess exposures that may be used in studies that capture information about susceptibility across the entire genome. Optimally, using new bioengineering approaches, exposures that an individual comes in contact with will be measured more accurately during critical time points. This program also will develop ways to measure an individual's response to these exposures using new molecular technologies. It is envisioned that these methods will provide measures of personal exposure that are quantitative, precise, reliable, reproducible, and that can be scaled up to implement in large population studies in the near future.

→ Lai M, et al. *Nanotechnology* 2009;20(18):185602. PMID: 19420618.
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Wang J, et al. *Small* 2008;4(1):82-6. PMID: 18081131.
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Mangal T, et al. *Chem Res Toxicol* 2009 May;22(5):788-97. PMID: 19309085. PMCID: PMC2684441.
Hsu PY, et al. *Cancer Res* 2009;69(14):5936-45. PMID: 19549897. PMCID: PMC2855843.
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Cheng AS, et al. *Cancer Res* 2008;68(6):1786-96. PMID: 18339859.
Emeny RT, et al. *Chem Biol Interact* 2009;181(2):243-53. PMID: 19576872.
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Sridhar S, et al. *BMC Genomics* 2008;9:259. PMID: 18513428. PMCID: PMC2435556.
Bharate SB, et al. *Bioorg Med Chem Lett* 2009;19(17):5101-4. PMID: 19640713. PMCID: PMC2728166.
Li B, et al. *Toxicol Sci* 2009;107(1):144-55. PMID: 18930948. PMCID: PMC2638647.
Nagy JO, et al. *Bioorg Med Chem Lett* 2008;18(2):700-3. PMID: 18086524. PMCID: PMC2839895.
→ For more information, see http://www.gei.nih.gov/exposurebiology/index.asp
→ (E) (**NIEHS**, NIDDK) (GPRA)

Nanotechnology

Researchers Levitate Object at a Microscopic Scale: Technique May Assist With Development of Nanotechnology: Similar to the way that like poles of magnets repel each other, certain combinations of molecules generate electrical forces that will prevent them from coming in contact with each other under certain conditions. Building on these concepts, researchers actually have levitated an object, suspending it without the need for external support. Working at the molecular level, the researchers relied on the tendency of certain combinations of molecules to repel each other at close contact, effectively suspending one surface above another by a microscopic distance. In their study, the researchers brought a tiny gold-plated sphere in contact with a flat glass surface, separating them with a liquid known as bromobenzene. At close distances, the molecular forces of the two surfaces, when in the presence of bromobenzene, repelled each other, so that the molecules of gold and glass never came in direct contact with each other and were separated by a few nanometers. The new technique may prove useful to the emerging field of nanomechanics—the development of microscopic machinery and even robots. By altering and combining molecules, tiny machines and even robots could be devised to perform surgery, manufacture food and fuel, and boost computing speed, operating free of friction.

→ Munday JN, et al. *Nature* 2009;457(7226):170-3. PMID: 19129843.
→ For more information, see http://www.nichd.nih.gov/news/releases/jan07-09-Levitate-Object.cfm
→ (I) (**NICHD**)

Nanotechnology in Cancer: Nanotechnology innovation has been driven predominantly by physicists, engineers, and chemists; progress in cancer research comes primarily from discoveries of biologists and oncologists. The NIH Alliance for Nanotechnology in Cancer has set a goal of creating a community of cancer nanotechnologists who work together to develop nanotechnology approaches; apply them to the prevention, diagnosis, and treatment of cancer; and educate the medical community about opportunities enabled by cancer nanotechnology. The Alliance organized a session at 2009 American Association for Cancer Research meeting on Cancer Diagnostics Using Nanotechnology Platforms. Participants included high-profile investigators who work on the development of new nanodevices for in vitro diagnosis and in vivo imaging and clinicians who define oncology applications of those devices. Examples of this work include: PRINT, a technique allowing for controllable fabrication of nanoparticles; researching novel diagnostic techniques for proteins and DNA; developing implantable nanosensors; researching novel nanoparticle-based imaging agents and nanosensors; and developing nanotechnology-based cancer screening tools.

→ For more information, see http://nano.cancer.gov/
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research*
→ (E/I) (**NCI**)

Nanotechnology Task Force: Nanotechnology deals with the understanding and control of matter at dimensions of approximately 1 to 100 nanometers, where unique phenomena enable novel applications. By applying cross-disciplinary methods from physics, material science, and engineering, NIH is shaping a new paradigm with vast implications for revolutionizing diagnostics, therapeutics, and personalized medicine. NIH initiated the Trans-NIH Nanotechnology Task Force for the purpose of (a) identifying scientific opportunities at the interface of nanotechnology, nanomedicine, and nanobiology; and (b) enhancing understanding of the health implications of engineered nanomaterials (ENMs) for biological systems. The Task Force tracks NIH investments in basic and applied nanoscale research, organizes national and international meetings, develops reports, participates in congressional hearings, and plays a key collaborative role in interagency activities. NIH has been named the Federal government's lead agency for coordination of Federal research on the health implications of nanotechnology under auspices of the National Nanotechnology Initiative's Nanoscale Science, Engineering, and Technology Subcommittee (NSET) and plays a key role in development of its Environmental, Health, and Safety Strategy.

→ For more information, see http://dpcpsi.nih.gov/collaboration/
→ (O) (**OSP/OSPA**, FIC, NCI, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)

Tracking Stem Cell Mobility Within Cardiovascular Tissues: Current cellular therapies suffer from low rates of cell engraftment due to the early destruction of cells. In 2007, in response to a program announcement, Innovative Application of Nanotechnology to Heart, Lung, Blood, and Sleep Disorders, NIH funded a grant to formulate a biocompatible cell encapsulation agent designed to protect and track mesenchymal stem cells for administration to patients. (Mesenchymal stem cells are the progenitors of all connective tissue cells). The investigators have demonstrated that encapsulation of mesenchymal stem cells improves long-term cell viability in cultures, and also have shown that the encapsulated cells can be detected using computed tomography or magnetic resonance imaging following in vivo injection. NIH is assessing the progress of the grant through an ongoing GPRA goal—by 2012, develop and apply clinically one new imaging technique to enable tracking the mobility of stem cells within cardiovascular tissues.

→ (E) (**NHLBI**)

Probing Proteins

Protein Structure Initiative (PSI): Scientists learn a lot by studying the detailed, three-dimensional structures of proteins. This knowledge helps them better understand the biochemical processes involved in health and disease. It also can greatly advance the design of medicines to treat a wide range of diseases. Recognizing this, NIH established PSI in 2000 to determine the structures of hundreds of novel proteins by means of high-throughput structure determination. In 2009, NIH announced plans for a new direction of the Protein Structure Initiative to be named PSI:Biology. The new program will support research partnerships between groups of biologists and high-throughput structure determination centers to solve problems of biomedical importance. In addition to benefiting the PSI team, this work will continue to accelerate research in other fields.

→ For more information, see http://www.nigms.nih.gov/Initiatives/PSI
→ (E) (**NIGMS**)

New Targets Identified for Intervention in the Development of Head and Neck Cancers: Over the last decade, cancer researchers have made significant progress in defining the molecular pathways involved in the development of head and neck squamous cell cancer. Studies that identify and characterize "key players" hold tremendous promise for the future treatment of these devastating cancers and ultimately improve the overall survival and quality-of-life for afflicted patients. One such key player is a family of proteins known as Wnt. Aberrant activation of the Wnt pathway has been found to be associated with cancer development and progression. Wnt promotes initiation of cancer by increasing the nuclear accumulation of ß-catenin, an integral component of Wnt signaling, to activate target genes downstream. However, the mechanism of ß-catenin recruitment to the Wnt target gene promoter largely is unknown. In an elegant study, the researchers discovered that ß-catenin interacted with two other molecules (commonly called TBL1 and TBLR1), leading to the recruitment of ß-catenin to the promoter of Wnt target genes. Decreasing TBL1 or TBLR1 via genetic knock-down did not affect the nuclear accumulation of ß-catenin, but it did inhibit ß-catenin significantly from binding to Wnt target gene promoter and the expression of Wnt target genes associated with tumor development. Moreover, depletion of TBL1 or TBLR1 inhibited invasive growth of tumor cells. These results provide fundamental knowledge about tumor genesis by revealing two new components required for nuclear ß-catenin function. Targeting these molecules can have important therapeutic implications for head and neck cancer.

→ Li J, Wang C-Y. *Nat Cell Biol* 2008;10(2):160-9. PMID: 18193033.
→ This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDCR**)

NIGMS/NCI Collaborative Access Team (GM/CA-CAT): Structural biology is a field in which scientists learn about molecules by determining their 3-D structures in atom-by-atom detail. Large user facilities called synchrotrons allow researchers to use X-rays to determine molecular structures more easily, quickly, and cheaply than ever before. Two NIH institutes (NIGMS and NCI) funded the development of a new experimental station at the Advanced Photon Source at Argonne National Laboratory. The new station includes three X-ray beamlines for use by scientists from across the United States to determine the detailed, three-dimensional structures of molecules. Two of these beamlines provide world-leading capabilities for X-ray diffraction data from very small protein crystals only a few microns in dimension. This research capability is important to understand basic biological processes and for drug design. The facility now is in full operation.

→ For more information, see http://www.gmca.anl.gov
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIGMS**, NCI)

Scientists Accomplish Initial Catalogue of the Human Salivary Proteome: Secretions from the major salivary glands (parotid, submandibular, and sublingual) contain many peptides and proteins. They contribute to saliva's important roles in maintaining oral health, including antimicrobial, lubricating, buffering, and digestive properties. Salivary gland disorders, which result in severe dry mouth, compromise quality of life because they often lead to decay and periodontal diseases, mucosal infections, halitosis, taste impairment, and difficulties in swallowing and speaking. Saliva is a complex fluid; over the years, a number of salivary proteins have been reported but a systematic approach to catalogue all the proteins present in saliva was only initiated in 2004. NIH supported three teams of investigators to conduct the first comprehensive analysis of the salivary proteome. After samples were collected and analyzed, the data were standardized and integrated, yielding a salivary proteome that comprises 1,166 proteins. Of these proteins, 152 parotid and 139 submandibular/sublingual proteins were identified by all 3 research groups; these proteins form the core proteome. Most proteins identified were extracellular or secretory proteins, and involved in numerous molecular and cellular processes. A significant number of proteins represented in the salivary proteome also have been found to exist in the plasma or tear proteomes. This initial catalogue of the salivary proteome is a significant first step toward a comprehensive understanding of what the functions of saliva are, and how salivary composition is dependent on physiological variations, including on health and disease. This proteome could be the source of potential diagnostic and prognostic biomarkers for oral and systemic conditions.

→ Denny P, et al. *J Proteome Res* 2008;7:1994-2006. PMID: 18361515.
→ This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDCR**)

Metabolic Network Model of a Human Oral Pathogen: The bacterium *Porphyromonas gingivalis* causes severe, chronic periodontal disease. Recently NIH-supported researchers constructed a complex metabolic network map for *P. gingivalis* with which to model the metabolic properties of all genomically identified components of the system. The scientists used a technique known as flux-balance analysis (FBA) to construct the model, which consisted of 679 metabolic reactions involving 564 metabolites. There was significant correlation between the model's predictions and the bacterium's experimentally observed metabolism. The true power of this model became apparent when "virtual knockouts" were employed to predict the effect of the loss of certain genes or metabolic pathways on growth rate, and the model very effectively predicted disturbances affecting biosynthesis of large molecules known as lipopolysaccharides. This is the first description of a model of this type for an oral periodontal pathogen. Still in their infancy, metabolic network models are a

logical extension of genome sequence data. They can provide the ability to perform virtual metabolic modeling of organisms with limited or no in vivo experimental histories. These models also could be applied to highly interdependent mixed microbial communities, including the oral microbiome, ultimately resulting in new biomedical applications. Such modeling greatly increases opportunities to discover new antibacterial drug targets. These studies provide new molecular targets for therapeutic drugs; they also can suggest the molecular mechanisms for virulence, intracellular persistence and survival, and ability of the bacteria to survive stresses from the (in this case, human) host defense mechanisms.

→ Mazumdar V, et al. *J Bacteriol* 2009;191(1):74-90. PMID: 18931137. PMCID: PMC2612419.
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIDCR**)

New Biomaterials System Programs Cells in situ to Fight Cancer: In the body's immune response to foreign invaders, dendritic cells signal and activate other cells to initiate a generalized inflammatory response. Cell-based cancer vaccinations build on this natural tendency by isolating and activating a patient's dendritic cells using tumor antigens, and then injecting the reprogrammed cells back into the patient. The activated dendritic cells travel home to the lymph nodes and promote an antitumor response. Unfortunately, most transplanted dendritic cells die. Additionally, reprogrammed cells partially lose their effectiveness after injection back into the body. Thus, multiple rounds of injections are required to achieve significant effect. To address these limitations, investigators developed a multifunctional in situ dendritic cell reprogramming system composed of polymeric biomaterials that release cytokines to attract dendritic cells already within the lymph nodes into the biomaterials. The dendritic cells are then activated by the biomaterials. The biomaterials reduce their cytokine release at a controlled rate so that after activation, the dendritic cells will migrate away from the biomaterials back home to the lymph nodes and present tumor antigens to T cells found there. In a mouse model this sophisticated system provided protection from tumor development equal or superior to that provided by traditional cancer vaccines without the complications and costs of ex vivo cell manipulation and transplantation. The new system also provided much better control over the number of dendritic cells than traditionally generated cancer vaccines. This study demonstrates a powerful new application for polymeric biomaterials that could be used in the future against cancers and other diseases.

→ Ali OA, et al. *Nature Materials* 2009;8(2):151-8. PMID: 19136947. PMCID: PMC2684978.
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NIDCR**)

Clinical Proteomic Technologies for Cancer: The Interagency Oncology Task Force (IOTF) held a workshop in October 2008, bringing together almost 60 participants representing NIH, FDA, industry, academia, and standards organizations. These key stakeholders in the proteomics community gathered to explore the regulatory requirements that will be needed to validate protein-based marker panels and any new technologies (hardware) for their intended use. Because there is a lack of guidance for multiplex proteomic assays, the workshop was an opportunity to engage CPTC scientists currently working through the issues that FDA will need to address when reviewing 510(k) submissions for proteomic technologies such as mass spectrometry and affinity arrays. FDA and the proteomic community posed relevant questions to each other with the goal of understanding the challenges and needs of each group. Outputs will include a publication on analytical validation issues that specific proteomic technologies should address when seeking FDA approval and mock 510(k) regulatory submissions for two technologies—mass spectrometry and affinity platforms. Together, these documents will help orient FDA to proteomic technologies in novel diagnostics and serve as a springboard for guidance to the proteomics community.

→ For more information, see http://proteomics.cancer.gov
→ For more information, see http://www.cancer.gov/newscenter/pressrelease/FDAGuidance
→ (E/I) (**NCI**)

Unique Compounds Added to Chemical Libraries: Potent, drug-like molecules that selectively bind to the kappa opioid receptor have potential utility in the treatment of drug addiction, depression, psychosis and dementia, pain, and even HIV infection. Well more than 100 unique, new molecules constructed independently by two NIH-supported groups have been found to provide entirely new classes of kappa opioid binders. These molecules are potent and display a diversity of pharmacological activities that are under intensive active investigation.

→ Beeler AB, et al. *J Comb Chem* 2005;7(5):673-81. PMID: 16153061.
→ For more information, see http://www.cmld.ku.edu/sbc_photos.shtml
→ For more information, see http://pdsp.med.unc.edu/indexR.html
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIGMS**) (GPRA)

Transforming Health Care

Neural Interfaces Program: Neural interfaces are systems that operate at the intersection of the nervous system and an internal or external device, including neural prosthetics. Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. NIH pioneered the development of this technology, beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants, which help people with hearing impairments; respiratory and hand grasp devices for people with spinal cord injuries; and deep brain stimulation for Parkinson's disease, among other contributions. Current work aims to restore voluntary bowel and bladder control and standing to spinal cord-injured persons, allow paralyzed persons to control devices directly from their brains, improve cochlear implants, and improve deep brain stimulation, which may be applicable to many brain disorders. Through the years, the program has fostered the development of a robust research community, now including private sector companies, and represents a cooperative effort among several ICs, which also coordinate their efforts with programs that now are underway in the Department of Veterans Affairs and Department of Defense.

→ For more information, see http://www.ninds.nih.gov/funding/research/npp/index.htm
→ For more information, see http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
→ (E) (**NINDS**, NEI, NIBIB, NICHD, NIDCD)

Molecular Theranostics: New Technologies for the Diagnosis and Treatment of Diseases: The concept of combining a therapeutic with a diagnostic agent rapidly is evolving and goes beyond traditional diagnostic tests that screen or confirm the presence of a disease. With specialized molecular imaging techniques and biomarkers, theranostics might predict risks of disease, diagnose disease, and monitor therapeutic response leading to real-time, cost-effective treatment. NIH supports a number of teams that are developing novel theranostics and approaches that can be applied in clinical studies of human patients. A team of chemists and neurosurgeons at the University of Michigan is developing highly specific, dye-loaded nanoparticles capable of delivering targeted photosensitizers to improve the survival of brain tumor patients. This technique will allow neurosurgeons to visualize the brain tumors for surgical resection of the main tumor mass while eradicating remaining tumor cells through a process known as photodynamic therapy. These particles also contain imaging contrasting agents to visualize response to therapy.

→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NIBIB**)

Edward R. Roybal Centers for Translation Research in the Behavioral and Social Sciences in Aging: NIH supports 13 Roybal Centers whose objective is to improve the health, quality of life, and productivity of middle-aged and older people by facilitating translation of basic behavioral and social science to practical outcomes by developing new technologies and stimulating new "use-inspired" basic research in the behavioral and social sciences. Roybal investigators have made several key discoveries. For example: One Center has developed tools and technologies for identifying older adults at risk for automobile crash involvement, and is working with industry partners to develop and disseminate products based on these tools. Another Center has developed two evidence-based interventions from its in-depth work on physical activity for older adults. One program, Fit and Strong!, is targeted to older adults with lower extremity osteoarthritis, and one is targeted to older adults with developmental/intellectual disabilities (primarily Down syndrome). A Roybal investigator has developed instruments for self-efficacy appropriate for use with older adults with developmental/intellectual disabilities; these have been adopted internationally. Finally, a Center has developed a "living laboratory" model methodology for in-home assessment of activity to facilitate early detection of changes in health or memory. Other companies have used this model to develop related products, and the model has spurred several new grant-funded research projects, including the development of a new medication tracker for older adults.

→ For more information, see http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/roybals.htm
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIA**)

Smart Coatings for Implanted Biomaterials: A major limitation on the longevity of vascular grafts and implanted materials stems, not from failure of the graft or material itself, but typically, from the body's rejection in the form of blood clots or refusal to integrate with surrounding tissue. Recently, new classes of polymer-based biomimetics that resemble the cell surfaces of healthy blood vessels have demonstrated excellent resistance to platelet adhesion, a major problem for implanted materials in contact with blood. These biomimetic polymers have undergone successful preliminary clinical testing, and the same approach now is being used to develop biomimetic coatings resembling other types of human tissue. This technology recently was acquired by a major medical implant manufacturer.

→ Kumar AM, et al. *J Am Chem Soc* 2008;130(4):1466-76.PMID: 18177047. PMCID: PMC2536642.
Larsen CC, et al. *Biomaterials* 2007;28(24):3537-48. PMID: 17507089. PMCID: PMC2034336.
→ This example also appears in Chapter 3: *Molecular Biology and Basic Research*
→ (E) (**NIBIB**)

Medical Technologies that Reduce Health Disparities: Appropriate medical technologies should be effective, affordable, culturally acceptable, and deliverable to those who need them. NIH is funding a research initiative to support the development of appropriate medical technologies for underserved settings. To ensure that the technology is appropriate, applications must involve interactions with underserved populations and/or collaborations with clinics in an underserved community.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-09-001.html
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIBIB**, NCMHD, NCRR, NIMH)

Research Training and Career Development

While the risk factors for heart failure—such as overweight, high blood pressure, and diabetes—have long been known, understanding its genetic origins is a much more recent pursuit and one of our most promising potential sources for novel drugs and therapies. Dr. Thomas Cappola was first drawn to this challenge during his medical residency when he began to study the molecular characteristics of the failing human heart. Over the next several years, NIH research training and career development awards helped provide him with the skills he would need to address such complex translational research questions. An opportunity to be a trainee on an institutional research training grant provided an in-depth exposure to patient-oriented research, and a clinical research curriculum award allowed his university to provide him with formal coursework in clinical investigation. Later support from the NIH loan repayment program permitted him to continue to pursue medical research without dwelling on the burden of repaying medical school loans, and an individual career development award provided protected time to further advance his research goals while working with a more senior investigator. This combination of NIH research training, loan repayment, and career development support has allowed Dr. Cappola to establish himself as an independent investigator pursuing his long-term research goal "to translate basic scientific discoveries into new approaches to treat and prevent heart failure," and in 2008, his use of genomic techniques to study heart failure was recognized with a Presidential Early Career Award for Scientists and Engineers.

Introduction

The biomedical and behavioral research conducted and supported by NIH—ranging from the very basic to the highly applied—has long been recognized as critical to advancing the quality of health care in the Nation and the world. As a result of NIH research, diseases such as AIDS, stroke, congestive heart failure, and diabetes increasingly are being treated or prevented more successfully. Further research undoubtedly will lead to new or improved medical therapies for a spectrum of diseases and disorders, but new advances in prevention, diagnosis, and treatment are dependent largely on the creativity, insight, and resources of the best scientists, and for these benefits to continue there must be a steady infusion of highly trained, well-equipped, and innovative new investigators. Research training is where cures begin.

Research training is where cures begin.

NIH research training and career development programs are designed to prepare new minds for research and ensure that diverse pools of highly trained scientists are available in sufficient numbers and with appropriate expertise to generate new discoveries, meet the needs of rapidly moving scientific field, and bring science to bear on complex and evolving health care challenges. By sponsoring research training and career development programs in universities, teaching hospitals, NIH laboratories, and other research-intensive settings, NIH expects that trainees and newly trained investigators not only will be exposed to the latest research findings and techniques, but also will be prepared to rise to the challenge of emerging problems in medicine and health. To further ensure that the research workforce will be poised to respond to evolving national and international public health needs, NIH takes steps to encourage individuals to focus on targeted or under-researched areas such as clinical and translational research, rare diseases, health disparities, and global health priorities.

The task of assessing and predicting research personnel needs across the entire spectrum—in the basic biomedical sciences, behavioral and social sciences, clinical sciences, oral health sciences, nursing research, and health services research—is daunting. Aligning the requisite expertise with public health needs is complicated by the evolving nature of biomedical, behavioral, and clinical research; the time required for research training; the international nature of research; and the mobility of the global research workforce. Preparing for a career in research generally requires a commitment of 8 to 10 years or more of predoctoral and postdoctoral training and career development; in the meantime, science is advancing, new diseases are emerging, and existing diseases are becoming better understood, diagnosed, and prevented.

In determining how best to sustain the continuing need for biomedical and behavioral scientists, NIH is guided by regularly scheduled analyses of the research workforce. Chief among these assessments are recurring studies conducted by the National Academies (NAS), which provide guidance on the fields in which researchers are likely to be required and on the number of new investigators needed in the basic biomedical, behavioral, and clinical sciences. NIH also routinely evaluates the outcomes of its training programs, comparing the subsequent research involvement of students and postdoctoral scholars who participate in NIH research training with their counterparts who were trained through other channels. Beyond such agency-wide assessments, individual ICs determine the need for new scientific personnel in mission-specific research areas through targeted evaluations, input from extramural investigators, and guidance from their national advisory councils.

NIH offers a broad range of research training and career development opportunities in its extramural and intramural research communities, through institutional training awards and individual fellowships, individual and institutional career development awards, continuing education, workshops, research grants, awards, and supplements to promote diversity or reentry into health-related research careers. Although its programs are largely directed toward graduate students and newly trained investigators, NIH offers a number of highly focused training and career development opportunities for individuals at other career stages, from college students to established scientists. NIH's research training and career development programs cover a broad range of basic biomedical, behavioral, and clinical research, including the interdisciplinary junctures between fields.

All NIH training and career development programs foster and encourage a diverse pool of participants. NIH expects that efforts to diversify the research workforce will lead to the recruitment of the most talented scientists from all groups, improved quality of the educational and training environment, more balanced and broader perspectives in setting research priorities, enhanced ability to recruit and retain subjects from diverse backgrounds into clinical research protocols, and improved capacity to address and eliminate health disparities. In addition to NIH's dedication to the inclusion of minorities and disadvantaged populations in the biomedical research workforce (also see the section on *Minority Health and Health Disparities* in Chapter 2), NIH is committed to the recruitment, retention, reentry, and advancement of women in biomedical research careers. Much progress has been made through the recent efforts of the NIH Director's Working Group on Women in Biomedical Careers. In response to recommendations from the Working Group and others, NIH extended the length of parental leave offered to NIH-sponsored trainees and fellows in 2008, and introduced the option for young scientists to pursue career development on a part-time basis in 2009.

NIH extended the length of parental leave offered to NIH-sponsored trainees and fellows in 2008 and introduced an option for part-time career development in 2009.

Catalogs of Research Training and Career Development Activities

In response to the mandate under SEC. 403 (a)(4)(C)(iv) of the Public Health Service Act to provide catalogs of research training activities, included here are live links to spreadsheets of:

- Funded Kirschstein-NRSA and National Library of Medicine *Institutional* Research Training Grants, FY 2008 and FY 2009
- Funded Kirschstein-NRSA and National Library of Medicine *Individual* Fellowship Awards, FY 2008 and FY 2009

Regarding postdoctoral scholars employed on research grants, NIH is implementing new reporting requirements. Grantees will be required to provide the names of all individuals associated with research projects for 1 or more months during the previous award year. In addition, individuals in postdoctoral roles will be required to establish and maintain personal profiles in the NIH eRA Commons. The Commons user ID for postdoctoral scholars will be reported in the list of individuals involved with NIH research projects. Information on postdoctoral scholars will be available for the next (FY 2010 and FY 2011) NIH Biennial Report.

Summary of NIH Activities

Extramural Programs and Progress: Research Training

Trans-NIH Programs and Initiatives

Training for a career in research typically requires a combination of specialized coursework and hands-on research experiences under the guidance of an established investigator. Most NIH-funded research training activities focus on predoctoral students and postdoctoral scholars and are provided either through training grants (T awards), which are awarded to institutions to support a coordinated program of training for a group of students or scholars, or fellowships (F awards), which directly support an individual's training. The principal NIH research training program for U.S. citizens and permanent residents, in size and breadth of coverage, is the Ruth L. Kirschstein National Research Service Award (NRSA) program. The goal of the NRSA program is to support promising students and postdoctoral scholars with the potential to become productive, independent investigators in fields relevant to NIH's mission. Training activities can be in basic biomedical or clinical sciences, in behavioral or social sciences, in health services research, or in any other discipline relevant to the NIH mission, and always include instruction in the responsible conduct of research. All ICs with funding authority award NRSA institutional research training grants and fellowships, except FIC and NLM. Reflecting the unique nature of their missions, the latter two ICs have distinct training authorities, separate from the NRSA program (see IC Programs and Initiatives below).

Through the NIH-wide program of NRSA institutional training grants and fellowships, NIH ICs supported nearly 16,400 graduate students and postdoctoral scholars at universities, teaching hospitals, and research centers in nearly every state in FY 2008. Institutional training grants form the core of NIH's research training programs, providing support to more than 80 percent of all NRSA program participants. Training grants play a particularly important role at the predoctoral level: approximately 60 percent of trainees are graduate students, often engaged in coursework and laboratory rotations in preparation for identifying an area of research for in-depth study. (See Appendix E for a breakdown on the demographics of NRSA participants and a summary of the number and type of doctoral degrees awarded to predoctoral NRSA recipients.)

Through the NIH-wide program of Ruth L. Kirschstein National Research Service Award institutional training grants and fellowships, NIH ICs supported nearly 16,400 graduate students and postdoctoral scholars at universities, teaching hospitals, and research centers in nearly every State in FY 2008.

Individuals interested in research training in universities or departments where there are no institutional training grants, as well as advanced students and postdoctoral scholars seeking tailored training opportunities, have the option of applying directly to NIH for an individual research training fellowship. NRSA fellowships provide recipients with valuable experience in initiating and testing their own research ideas before becoming full-fledged investigators.

Across NIH, NRSA training grants and fellowships help ensure the diversity of the research workforce by including features designed to provide research training opportunities to individuals from populations and backgrounds typically underrepresented in research (also see the section on *Minority Health and Health Disparities* in Chapter 2). Because part of the inherent challenge of recruiting talented individuals into research training programs is to have a pool of prepared applicants from which to draw, NIH offers undergraduate research training to honors students at selected institutions who have an explicit interest in a research career and intend to pursue postgraduate education leading to the Ph.D., M.D./Ph.D., or other combined degree. At the graduate and postdoctoral levels, NIH policy requires institutional training grant directors to take steps to recruit and retain trainees from underrepresented groups, including racial and ethnic groups and individuals with disabilities.[57] Through the Ruth L. Kirschstein NRSA Individual Predoctoral Fellowship (F31) to Promote Diversity in Health-Related Research, NIH also provides graduate students from underrepresented groups with opportunities to pursue research training through individual fellowship awards.

The relative diversity of research training participants reflects NIH's commitment to cultivating a broad-based scientific workforce. Among FY 2008 trainees and fellows who reported their race and ethnicity, 66 percent were white, 14.9 percent were Asian, 7.6 percent were African American, 7 percent were Hispanic, 1 percent were Native American, and 0.7 percent were Native Hawaiian or Pacific Islanders. More than 51 percent of trainees and fellows in FY 2008 were women.

NRSA training grants and fellowships may target broad-based or field-specific research training, depending on the needs identified by the administering IC. In recent years, this flexibility has allowed the NRSA program to respond to interest in greater integration of training activities across NIH to fulfill workforce needs shared by multiple ICs. The result has been a series of trans-NIH research training initiatives through the NIH Roadmap for Medical Research and other channels.

As the early Roadmap research training initiatives have matured, some have been selected for continuation and further expansion. The most notable of these are the Roadmap training grants and institutional career development awards in clinical and translational research that have been assimilated into Clinical and Translational Science Awards (CTSA). The CTSA program aims to accelerate the development of new treatments by transforming the way clinical and translational research are conducted. Creating multidisciplinary research teams that include physicians, basic scientists, statisticians, specially trained research nurses, informatics experts, and other specialists is central to this transformation. The CTSA program will grow through 2011 to serve about 60 academic sites, providing research training and career development opportunities in areas such as clinical research design, epidemiology, biostatistics, pharmacology, biomedical informatics, behavioral science, and ethics to more than 1,200 NRSA trainees and new investigators. (CTSA trainees are included in the NRSA data provided in Appendix E.)

In addition to its formal research training programs, NIH supports graduate and postdoctoral research experiences on research grants. Though not an NIH "program" per se, the impact of this support is significant. Graduate students and postdoctoral scholars acting as research assistants gain knowledge, skills, and experience that help prepare them for careers in research. To provide a better understanding of how many graduate students and postdoctorates contribute to research through roles as assistants, NIH investigators will be asked to identify all research project personnel beginning in FY 2010. At that time, all postdoctoral scholars also will be expected to have established accounts in the Electronic Research Administration (eRA) Commons, a Web-based system through which NIH administers grants and collects demographic and other information about its community of investigators. With the implementation of these changes, NIH will have much greater understanding of the overall biomedical research workforce supported by its funding.

To provide a better understanding of how many graduate students and postdoctoral fellows contribute to research in their roles as assistants, and to the overall workforce involved in NIH research, NIH investigators will be asked to identify all research project personnel beginning in FY 2010.

IC Programs and Initiatives

Because each NIH IC has its own particular research mission, individual ICs are responsible for determining how the workforce needs identified by NAS and others apply to their specific scientific fields, selecting individuals and institutions for NRSAs or other research training awards to meet the needs identified, and reviewing annual progress toward building or enhancing capacity in the research workforce. Areas targeted for research training initiatives reflect the full array of NIH interests, from basic research training in biology and chemistry to clinical and translational research training in fields as distinct as cancer, infectious diseases, and aging. To ensure a supply of investigators attuned to the challenges of both research and patient care, a number of ICs also make awards for M.D./Ph.D. and other types of dual-degree training. The oldest and largest of these is the NIGMS Medical Scientist Training Program, which supports exceptional students pursuing an integrated program of graduate training in the biomedical sciences and clinical medicine.

While focusing on and supporting activities that address their respective missions and disease areas, ICs follow NIH-wide guidelines for NRSA research training and frequently collaborate to sponsor specific initiatives where there are overlapping interests or to stimulate interest in emerging fields. For example, eight ICs have partnered to support predoctoral training in biostatistics, through a program that integrates in-depth training in statistical theory and methodologies with basic biomedical, epidemiological, clinical, and behavioral research. In the area of neuroscience, multiple ICs support NRSA institutional training grants to provide broad neuroscience training for graduate students in the first and second years of study through the Jointly Sponsored Predoctoral Training Program in the Neuroscience. This program is affiliated with the NIH Blueprint for Neuroscience Research, a framework that brings together the 16 ICs and Offices that support neuroscience research and training, and provides a channel for coordinating their efforts. Other areas where ICs have come together to support research training on topics of joint interest include training at the interface of the behavioral and biomedical sciences, women's health, and bioethics.

NLM's research training portfolio generally parallels the structure and requirements of the NRSA program and reflects NLM's unique role as the primary Federal sponsor of biomedical informatics research and training. Like the ICs that provide NRSA research training, NLM prepares the next generation of informatics researchers and health information specialists through institutional grants (T15s), which support graduate and postdoctoral training in a broad range of topics, including health care information, bioinformatics, systems biology, imaging informatics, and public health informatics. NLM also offers a clinical informatics fellowship on the NIH campus designed to attract physicians and others to NIH to pursue research in clinical informatics. Unlike NRSA research training awards, some NLM training programs are open to master's degree holders seeking further graduate-level coursework and hands-on training. (Also see the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3.)

Reflecting the FIC mission to foster global health research and build research capacity in the developing world, FIC institutional training grants (D43s) differ from those offered by the NRSA program or by NLM by allowing a broader range of participants and emphasizing the development of institutional partnerships and collaborations between U.S. and international universities and scientists. Most FIC research training programs focus on providing research training to individuals from low- and middle-income nations, but a number of selected programs provide opportunities to U.S. students and postdoctoral scholars interested in international health research. FIC training programs are contributing to the building of sustainable research capacity in the developing world to enhance prevention, treatment, and control of infectious diseases, including HIV/AIDS, TB, and malaria, which are major causes of morbidity and mortality in those regions. Other FIC programs target research training in the areas of clinical, operational, and health services research; noncommunicable diseases; population studies; environmental and occupational health; trauma and injury; bioethics; and informatics training for global health. In order to foster long-term scientific partnerships between U.S. and foreign investigators and build research capacity, most FIC training grants require a joint collaboration between a U.S. and foreign institution.

Reflecting the FIC mission to foster global health research and build research capacity in the developing world, FIC institutional training grants emphasize the development of institutional partnerships and collaborations between U.S. and international universities and scientists.

Strength of Partnerships

Research training involves collaboration between NIH and its grantee institutions in the form of shared responsibilities and funding. In making NRSA training grant awards, for example, NIH relies on universities and other sites that receive support to select the best trainees, determine the curriculum and other aspects of the training program, and provide mentorship and supplemental funding to participating students and postdoctoral trainees. Although NRSA fellowships are targeted to individual students or postdoctoral scholars, NIH expects the sponsoring institutions to provide fellows with experienced mentors and supplemental research funding support. In some targeted NRSA research training programs, NIH also partners with other agencies, private foundations, and professional societies to achieve shared research training goals.

Partnerships between NIH and the private sector are helping to accelerate research training in creative ways. For example, NIH has partnered with the Howard Hughes Medical Institute to develop new graduate student training programs at the intersection of the biological and physical sciences and engineering. Through a distance-learning partnership, NIH has joined with Duke University School of Medicine to offer the Master of Health Sciences in Clinical Research degree to fellows and others on the NIH campus; to date, more than 65 individuals have completed the program. (Also see the section on *Clinical and Translational Research* in Chapter 3.)

NIH Training Program Evaluations and Assessments

Since the NRSA program was established in 1974, NIH training programs have been regularly reviewed and evaluated. NAS has undertaken regular reviews of the medical research workforce and made recommendations for modifications in the size and focus of the NRSA program. In addition, NRSA program processes and outcomes are regularly assessed through recurring program evaluations and annually measured against several Government Performance and Results Act (GPRA) goals. These reviews have been coordinated by OER, which oversees the NRSA program. Increasingly, however, individual ICs also are undertaking evaluations of their specific NRSA and other research training programs.

NAS Reviews. Over the past 30 years, the NRSA program has been the subject of more than a dozen studies by NAS, which has provided expert guidance on the fields in which researchers are likely to be required and on the number of new investigators needed in the basic biomedical, behavioral, and clinical sciences. The most recent NAS report on research training, published in 2005, noted that the NRSA program sets the standard for the entire research training establishment, attracting high-quality students into research and into fields of particular need.[58]

The recurring nature of these NAS studies—the next will be issued in 2010—ensures that NIH research training programs reflect changes in science and research needs that inevitably occur over time. In recent years, NIH has followed recommendations from NAS committees for enhancing stipend levels, promoting the early completion of research training, and improving workforce data collection and analysis.

Evaluations of NRSA Training. Evaluations of the outcomes of NRSA research training routinely have found that graduate students participating in NRSA programs complete their degrees faster, are more likely to pursue research careers, and have greater subsequent success in research than do students not participating in NRSA programs.[59] Similarly, a 2006 evaluation of NRSA postdoctoral training found that NRSA postdoctoral fellows were more likely to successfully pursue research careers. More than 60 percent of former NRSA postdoctoral fellows who subsequently applied for a major NIH research grant received funding, compared to 36 percent of other postdoctoral fellows.[60]

Government Performance and Results Act (GPRA) Goals. Every year, NIH assesses NRSA research training outcomes and program management against two goals established under GPRA. In the first of these goals, NIH seeks to measure the quality of its programs and ensure that substantial numbers of trainees and fellows are retained in research careers by comparing the proportion of former NRSA trainees and fellows who apply for and successfully receive NIH research grant support against their peers. Subsequent NIH support is one of several measures that reflect the impact of NRSA research training on participants' ability to successfully pursue and sustain a research career. To date, NIH has always met this GPRA goal, because NRSA trainees and fellows consistently outperform their counterparts.

The second training-related GPRA goal measures NIH progress in improving the efficiency of NRSA program management by developing and implementing the xTrain electronic system for appointing trainees to institutional training grants. Since its introduction in 2008, the number of universities using the xTrain system has tripled to more than 65, and in 2009 nearly 11 percent of training appointments were made electronically. Despite the substantial growth in institutions using xTrain, however, the number of appointments submitted electronically did not meet NIH's GPRA goal for FY 2009. As a result, NIH plans to begin requiring institutions to use xTrain to submit appointments to selected training grants in FY 2011, and continues to expect that the new system will be fully implemented by FY 2012, with 100 percent of trainees appointed to training grants electronically rather than through paper appointment forms. Ultimately, xTrain is expected to

save substantial staff time and eliminate data entry errors while increasing NIH's efficiency and enhancing the integrity of data used for program monitoring and evaluation purposes.

Institute and Center Training Evaluations. In addition to scheduled NIH-wide assessments of programs coordinated through OER, individual NIH ICs undertake periodic, targeted evaluations to improve implementation and assess outcomes of their own training programs. Institute-specific evaluations typically focus on research training needs in particular areas and often are conducted by independent "blue ribbon" panels of scientific leaders from around the country. For example, in 2008, NIMH convened a workgroup, composed of Advisory Council and outside experts, to evaluate its research training programs and make recommendations for future directions. Other recent and ongoing IC assessments include evaluations of the outcomes of the NIDDK research training fellowships and career development awards, CTSA training grants, and NIAMS research training programs. Details of these evaluations are provided in the Notable Examples below.

Extramural Programs and Progress: Career Development

Given the pace at which science advances, novel techniques and methods are introduced, and new fields emerge, investigators need opportunities to fully develop their scientific expertise and stay up to date. NIH Career Development Awards (K awards) address that need. Collectively, more than a dozen types of K awards support investigators as they establish their research careers, pursue new directions, or dedicate themselves to training and mentoring the next generation of scientists. Like the T and F training awards, some career development awards support institutional activities to nurture careers and others directly support individual development.

Many career development awards are designed for researchers at specific career stages, particularly newly trained investigators. The NIH-wide Pathway to Independence Award accelerates the transition from mentored to independent research by providing a bridging mechanism, through which an initial 1- to 2-year mentored period is followed by an independent phase, during which awardees establish their own research programs and apply for independent research support. Other "mentored" career development awards provide support for a sustained period of protected time for intensive research career development under the guidance of an experienced investigator. The expectation is that, with this experience, awardees will be able to take the final steps toward establishing independent research careers and becoming competitive for new research project grant funding. For example, NIH supports the Building Interdisciplinary Research Careers in Women's Health program, which pairs junior faculty with senior investigators in an interdisciplinary environment. At the other end of the career spectrum, a number of ICs provide Senior Scientist Research and Mentorship Awards. These awards provide salary support for outstanding senior scientists and recognized leaders so that, through an interval of protected time, they can focus intensively on their research and mentor new investigators.

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Several career development awards are particularly designed to foster the involvement of clinicians in research. The Mentored Clinical Scientist Research Career Development Award continues a long-standing NIH commitment to provide support and protected time to individuals with clinical doctoral degrees so that they can engage in an intensive, supervised research career development experience. The award supports both didactic study and mentored research for individuals with a wide variety of clinical degrees, including the M.D., D.D.S., D.V.M., and Pharm.D. A related program, the Mentored Patient-Oriented Research Career Development Award, supports the career development of clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research.

Other career development programs target specific areas of science. Examples include the Career Enhancement Award for Stem Cell Research, which enables investigators to acquire new research capabilities in the use of human or animal

embryonic, adult, or cord blood stem cells, and the Mentored Quantitative Research Career Development Award, which encourages investigators from quantitative science and engineering fields to focus on questions of health and disease.

Coordination and Oversight by the NIH Office of Extramural Research

Much as NIH collaborates with grantee institutions in conducting research training, OER also partners with ICs to coordinate and monitor awards for research training and career development across NIH. With active input from the ICs, OER establishes and implements policies and guidelines for each of the programs; determines broad national needs for basic biomedical, behavioral, and clinical research personnel; coordinates NIH-wide evaluations; develops trans-NIH research initiatives in which NIH ICs participate; and develops and maintains information systems to enhance program efficiencies. OER convenes monthly meetings of the NIH Training Advisory Committee to provide an agency-wide forum to identify and discuss issues related to research training and to provide opportunities to coordinate activities pertinent to the review, administration, management, and evaluation of training grants and fellowships.

Intramural Activities

The NIH intramural program provides opportunities for students, postdoctoral scholars, and clinicians to gain research experience within the more than 1,100 NIH intramural laboratories. A multifaceted array of programs provides a vibrant, scholarly environment and ensures strong research training experiences for future investigators and the continued professional development of intramural scientists.

Among the intramural program's offerings are summer internships for high school, college, and graduate students. Recent college graduates who plan to apply to graduate or professional school also can spend a year engaged in biomedical research working side by side with NIH scientists. Current graduate students can spend a summer, or even a year, as fellows engaged in biomedical research at NIH. The Graduate Partnerships Program (GPP) enables students to pursue research at NIH toward their degrees in partnership with a participating academic institution. By linking academic environments with the breadth and depth of research at NIH, the GPP creates a valuable graduate experience, one that purposefully focuses on skills of the future scientist and how discoveries will be made in the decades ahead. The Clinical Research Training Program (CRTP) is a yearlong program designed to attract the most creative, research-oriented medical and dental students to the NIH campus. CRTP fellows spend a year engaged in a mentored clinical or translational research project in an area that matches their personal interests and goals.

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Training opportunities continue when scholars gain their graduate degrees. Year-round, NIH intramural laboratories employ fellows from the United States and abroad, creating a thriving, multidisciplinary intramural research community. The Postdoctoral Intramural Research Training Award provides the opportunity for recent doctoral degree recipients, who are U.S. citizens or permanent residents, to enhance their research skills in the NIH intramural environment. Trainees pursue both basic and clinical research. A parallel program, Visiting Fellowships, serves foreign national doctoral-level scientists. For clinicians, there are opportunities for residency and subspecialty training, including graduate medical education (GME)-accredited programs (for program completion data, see Appendix E). These GME programs enable research-oriented clinicians to weave research experience and training into their post-medical school training.

In recent years, NIH's intramural program increasingly has focused on helping graduate students and postdoctoral fellows develop their career skills. To ensure that intramural trainees and fellows can successfully advance in their careers, NIH offers courses in scientific writing and grant writing, as well as presentation and teaching skills. In addition, intramural trainees and fellows—indeed, all members of the NIH community—benefit from access to a plethora of NIH courses, seminars, and science career resources. For example, every day across the NIH campus there are scientific seminars and

colloquia addressing the latest developments and discoveries in biomedical science; meetings of more than 100 Scientific Interest Groups that host forums and lecture series on cutting-edge issues of interest ranging from the Bioethics Interest Group to the Integrative Neural Immune Interest Group; and short- and long-term course offerings such as "Introduction to the Principles and Practice of Clinical Research" and "Principles of Clinical Pharmacology."

NIH Loan Repayment Programs

The NIH Loan Repayment Programs (LRPs) are a vital component of our Nation's efforts to attract eligible doctoral-level professionals to research careers in fields of special importance—clinical, pediatric, health disparities, contraception and infertility, and AIDS research. To encourage qualified scientists to pursue research in these critical areas, the LRP provides financial assistance for educational debt in exchange for a 2- or 3-year research commitment. Nearly 1,600 program participants each year receive up to $35,000 annually in loan repayment and fulfill their commitments by conducting research in nonprofit, university, or government settings, or as an NIH employee.[61] A 2009 evaluation[62] of extramural LRP participants found that a substantial percentage remain in the research workforce after receiving a loan repayment award, and go on to receive subsequent research grants from NIH.

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Conclusion

The initiatives and program reviews highlighted in the next section demonstrate NIH's ongoing commitment to building and maintaining a biomedical, behavioral, and clinical research workforce that can uncover new knowledge that will lead to better health for all Americans.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Trans-NIH Research Training Programs

Ruth L. Kirschstein National Research Service Award (NRSA) Program: The Kirschstein-NRSA program is the primary route through which NIH provides research training to students and postdoctorates and ensures that a workforce of skilled investigators will be available to meet the Nation's needs in biomedical, behavioral, and clinical research. The program offers two modes of research training:

- NRSA Institutional Research Training Grants support predoctoral and postdoctoral research training programs at domestic institutions of higher education. Institutional research training grants allow universities, research institutes, and teaching hospitals to select specific trainees and develop a curriculum of study and research experiences tailored to provide high-quality research training. The training grant award provides stipends and offsets the cost of tuition for appointed trainees.

- NRSA Individual Fellowships provide support to promising students and postdoctoral researchers with the potential to become productive, independent investigators. Before applying, prospective fellows must identify a sponsor, who will help them develop into independent researchers. The individual fellowship award provides a stipend to the recipient, plus additional funds for tuition and an institutional allowance, which can be used for travel to scientific meetings.

→ For more information, see http://grants.nih.gov/training/nrsa.htm
→ For more information, see http://grants.nih.gov/training/T_Table.htm
→ For more information, see http://grants.nih.gov/training/F_files_nrsa.htm
→ (E) (**OER**)

Training M.D./Ph.D.s and Other Clinician Scientists: Investigators who are trained as both clinicians and scientists have long played a unique and vital role in health-related research. To ensure a continuing supply of these specially trained clinician investigators, NIH supports dual-degree training through dedicated NRSA awards, providing M.D./Ph.D. training through institutional Medical Scientist Training Program (MSTP) grants, and M.D./Ph.D. and other types of dual-degree training through individual predoctoral fellowship awards. More than 1,000 students per year receive dual-degree training through NRSA training grants and fellowships. By integrating clinical and research training, dual-degree programs allow participating students to launch their research careers much more quickly than would otherwise be the case.

→ For more information, see http://www.nigms.nih.gov/Training/InstPredoc/PredocOverview-MSTP.htm
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-09-232.html
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-09-232.html
→ (E) (**NIGMS**, NHLBI, NIA, NIAAA, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIMH, NINDS, ODP/ODS)

Training Activities of the Clinical and Translational Science Award Program: Clinical research requires unique skills in addition to those needed to care for patients, so academic health centers must equip members of clinical research teams with the special training and experience they need to succeed. NIH expanded its clinical research training programs through Roadmap T32 and K12 programs that largely have been assimilated into Clinical and Translational Science Awards (CTSAs). Clinical research trainees learn the skills needed to cultivate multidisciplinary research team collaborations and design research projects to compete successfully for funding in a mentored environment. The CTSA training program already is providing more than 1,000 research training and career development opportunities in multiple individual disciplines. As mandated in Section 106 of the National Institutes of Health Reform Act of 2006 (Pub. L. No. 109-482), NIH will evaluate the outcomes and effectiveness of the CTSA training programs. The evaluation will include surveys of trainees, scholars, and mentors and will address pediatric clinical research training issues. In addition, the evaluation will conduct secondary analyses of pediatric clinical research training data collected by the CTSA program. This is part of a much larger comprehensive evaluation of the CTSA program as a whole. Each individual CTSA recipient also evaluates his or her own training activities, and the CTSA Education/Career Development Key Function Committee provides a forum in which best educational practices can be identified. The CTSA program was initiated in September 2006, so the long-term impact of the CTSA program will not be known for 7 or more years. However, short-term process milestones and intermediate outcomes are expected in 1 to 7 years. For example, the CTSA consortium defined training standards for core competencies in clinical and translational research. The consortium identified the skills, attitudes, and knowledge that investigators need to participate successfully in multidisciplinary teams of clinician-scientists.

→ For more information, see http://nihroadmap.nih.gov/clinicalresearch/overview-training.asp
→ For more information, see http://www.ctsaweb.org
→ For more information, see http://www.ncrr.nih.gov
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**, Common Fund - all ICs participate)

NIH Roadmap Training for a New Interdisciplinary Research Workforce: As science has advanced over the past decade, it has become apparent that traditional organization of health research may, in some instances, slow the pace of scientific discovery. To foster changes in academic culture and interdisciplinary team approaches to research, in FY 2004, NIH announced several research training initiatives to provide interdisciplinary training to investigators at a range of career stages. One of these initiatives, the Interdisciplinary Health Research Training program, enabled institutions to develop postdoctoral training programs to provide newly minted scientists with interdisciplinary coursework and research training in fields outside their own, for example by integrating behavioral and/or social sciences with more traditional biomedical sciences research. A related program supported faculty interested in developing innovative and interdisciplinary courses, curricula, and education approaches. A final research training initiative, Training for a New Interdisciplinary Workforce, used a novel grant mechanism, the T90/R90, to support integrated interdisciplinary training at the undergraduate, graduate, and post-doctoral levels. Participants in this program all received training in at least two disciplines and had co-mentors from different fields. As Roadmap support for these programs nears an end, NIH announced in the summer of 2009 that the T90/R90 training and education award would be available for continued use by all NIH ICs.

→ For more information, see http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp
→ (E) (**NIDA**, Common Fund - all ICs participate)

Blueprint Interdisciplinary Research Training: Under the auspices of the NIH Blueprint, interdisciplinary training programs have been established in computational neuroscience, neuroimaging, and translational research in the neurobiology of disease.

- The computational neuroscience programs seek to attract undergraduate and predoctoral students from the physical, mathematical, and engineering sciences to neuroscience research, and to expand the training of neuroscience students in quantitative sciences. Students learn how to develop models of neural systems or processes, test them experimentally, and then use experimental data to refine the models.
- The neuroimaging programs support predoctoral students and summer research intensives and provide comprehensive training in the breadth of imaging techniques and their application to neuroscientific questions. The goal of these programs is to train the next generation of neuroimaging researchers in the limitations, advantages, and underlying principles of currently available neuroimaging modalities.
- The translational research programs support students at multiple stages of their careers. The programs are designed to cross-train students in basic and clinical neuroscience, focusing not on specific diseases but on the biological mechanisms that are shared across diseases.

These Blueprint training programs are successfully seeding the field of neuroscience with highly qualified graduate students, postdoctoral fellows, and faculty.

→ For more information, see http://neuroscienceblueprint.nih.gov/neuroscience_resources/training.htm
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIH Blueprint**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

Intramural Training and Education: Working in collaboration with the NIH Fellows Committee, the Graduate Student Council, and IC training directors, the NIH Office of Intramural Training and Education has instituted several major annual events to serve trainees in the Intramural Research Program.

- The NIH Career Symposium provides an opportunity for NIH graduate students and postdoctoral trainees to learn about the various career opportunities available to them and to explore factors that lead to career success.

- The Graduate & Professional School Fair enables representatives of graduate and professional schools to recruit our college-age trainees. At the same time, workshops on writing personal statements, interviewing, and applying to positions are offered to the trainees.
- The International Opportunities Expo invites embassies, foreign funding agencies, and global corporations to recruit individuals interested in careers outside the United States.
- The NIH National Graduate Student Research Festival is a 2-day event held on the NIH campus to recruit the best graduate students to postdoctoral positions in the Intramural Research Program.

→ For more information, see http://www.training.nih.gov/
→ (I) (**OIR**)

The NIH Working Group on Women in Biomedical Careers: The Working Group was established as a trans-NIH committee by the NIH Director in response to the National Academies report *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, and to address the concerns of NIH intramural women scientists. The Working Group, co-chaired by the Director, NIH, and the Director, ORWH, is developing innovative strategies to promote the advancement of women in research careers at the NIH and throughout the extramural community. The Working Group has held two national meetings: the National Leadership Workshop on Mentoring Women in Biomedical Careers, and Women in Biomedical Research: Best Practices for Sustaining Career Success, the recommendations from which are being incorporated into new initiatives. An RFA, Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Research, which will bring new insights for enhancing the efficacy of career development and mentoring programs for women, was developed and 14 awards were funded. Through the efforts of the Working Group, NIH extended the parental leave period for intramural trainees and NRSA recipients to 8 weeks and helped establish the Mid-Atlantic HERC, an online listing of positions at member institutions that is searchable using two sets of criteria to assist dual career couples. The NIH tenure clock has been extended to accommodate family leave, and a mechanism has been developed to employ a temporary lab manager to continue lab operations during extended leave of an intramural investigator. The Working Group also is developing initiatives to promote bioengineering as a career choice for women.

→ For more information, see http://womeninscience.nih.gov/
→ For more information, see http://www.midatlanticherc.org/
→ (E/I) (**ORWH**, NCI, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDCR, NIGMS, NINDS, NINR, NLM, OCPL, OD, OER, OIR)

Gauging the Role of Postdoctoral Researchers and Others in the Biomedical Workforce: To gain a better understanding of the size and characteristics of the biomedical research workforce, NIH is taking steps to identify all personnel involved in NIH research grants. Beginning with annual progress reports submitted in January 2010, NIH-funded investigators will be required to report on all personnel who have contributed a month or more of effort to their research projects, including postdoctoral researchers. In addition, postdoctoral researchers supported by research grants will be required to establish NIH Commons accounts, which will provide NIH with the ability to collect and report demographic information, such as gender, race, and ethnicity. These changes will provide a more complete picture of the research workforce supported by NIH and will enhance future evaluations of NIH training programs.

→ (E) (**OER**)

Extramural Loan Repayment Programs: Since they were established in FY 2000, NIH's extramural loan repayment programs have helped retain more than 4,500 new doctorates in research careers by repaying some or all of their educational debt. Most of the new applicants are early career researchers (within 6 years of terminal degree) with significant educational debt; in the most recent award cycle, median educational debt for new M.D. applicants was

$146,978. An early evaluation of the programs recently confirmed that program participants—the majority of which are M.D.s and M.D./Ph.D.s—are more likely to remain in the NIH-funded research workforce and to receive subsequent research grants from NIH.

→ For more information, see http://www.lrp.nih.gov
→ (E) (**OER**)

International Bioethics Education and Career Development Award Program: Few developing country institutions provide formal education in research ethics, and there are only a small number of developed country programs for advanced research ethics education/training focus in depth on the internationally relevant aspects of research ethics. Therefore, few developing country scientists and health professionals conducting clinical or public health research have received extensive education and training in the principles of research ethics, international codes and legal aspects of ethical research, informed consent, elements of study design that affect the ethical conduct of research, and the ethical framework for provision of care and risk/benefit analysis for study participants. NIH's response to this was to develop a research bioethics training grant program that focuses on training ethicists who understand the fundamental principles and the cultural nuances of these principles as manifested in the guidelines being developed by other international organizations. Launched in March 2000, the International Bioethics Education and Career Development Award program is an institutional training grant that enables academic institutions to develop or expand current graduate curricula and training opportunities in international bioethics related to performing research in developing countries. Since 2001, more than 180 trainees from 40 developing countries have participated in the training programs.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-04-001.html
→ (E) (**FIC**, NCCAM, NHGRI, NHLBI, NIAID, NIDA, NIDCR, NIEHS, NIGMS)

NIH/FIC Clinical Research Training Scholars and Fellows Program: In response to a call from the President to invest in the economy by investing in global health research, as well as the growing interest in global health on U.S. graduate school campuses, FIC has expanded its Clinical Research Training Scholars and Fellows program, now in its fifth year, to provide early career mentored opportunities for U.S. postdoctorates and senior graduate students in the health sciences. The purpose of the program is to encourage the next generation of clinical research investigators to gain research experience working to address international health issues. The program provides new investigators with hands-on experience working in poor and transitional countries.

This program, which offers one year of mentored clinical research training at a site in the developing world, gives international opportunities to U.S. trainees, with the hope that such experiences during a formative period will encourage them to pursue careers in global health-related clinical research. The program, now expanded, provides support for clinical research training activities at the foreign sites, as well as a stipend for a foreign graduate student to be trained in tandem with the U.S. trainee during the clinical research year. Since the start of the program, the stipend amount has significantly increased to enable foreign site scholars to participate in the clinical research experience for a full year. In 2008, FIC expanded its commitment to the program and funded 33 U.S. scholars and 33 international scholars, 8 more U.S. and 9 more international scholars than the previous year.

→ For more information, see http://www.fic.nih.gov/programs/training_grants/nih_fogarty.htm
→ (E) (**FIC**, NCI, NCMHD, NIAID, NICHD, NIDA, NINR)

Framework Programs for Global Health—A Signature American Recovery and Reinvestment Act Project: In response to the growing interest in global health on U.S. college campuses and to further build the multidisciplinary teams and curriculum needed to address global health issues, NIH has used some of its American Recovery and Reinvestment

Act (ARRA) funding to enhance the Framework Programs for Global Health (FRAME). FRAME builds global health research capacity in the United States and in low- and middle-income countries by supporting the development of innovative, multidisciplinary global health programs. Through the FRAME program, institutions create administrative frameworks to network multiple schools (such as engineering, business, arts and sciences, law, communications, public health, medicine, environmental studies, and others) on one or more campuses to address global health issues and to develop multidisciplinary global health curricula for undergraduate, graduate, and professional school students. Each program leverages and enhances currently funded global health projects at the institution and encourages new training opportunities, collaborations, and research. Institutions may choose to partner with other institutions anywhere in the world to plan joint curricula, interactive programs, and even joint degrees. Specifically, ARRA funding will bolster Framework Programs for Global Health at Dartmouth University, Yale University, the University of California at Irvine, and the University of New Mexico.

→ For more information, see http://www.fic.nih.gov/programs/training_grants/framework/index.htm
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-08-001.html#Section1
→ For more information, see http://www.nih.gov/news/health/may2009/fic-12.htm
→ (E) (**FIC**, NCI, NIBIB, NICHD, NINDS) (ARRA)

IC-Specific Programs and Initiatives

Predoctoral Research Training in Biostatistics: A workforce of biostatisticians with a deep understanding of statistical theory and new methodologies is vital to meet the biomedical, clinical, and behavioral research needs of the United States. With that end in mind, NIH has funded 13 predoctoral training programs in biostatistics to support 47 predoctoral trainees. The training program integrates biostatistical theory and evolving methodologies with basic biomedical research, including bioinformatics, genetics, molecular biology, cellular processes, and physiology, as well as epidemiological, clinical, and behavioral studies.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/par-04-132.html
→ (E) (**NIGMS**, NCI, NHGRI, NHLBI, NIAID, NIDCD, NIDCR, NINDS)

Training for Cancer Research: The Center for Cancer Training is preparing a workforce to advance cancer research through a scientifically integrated approach. The Center coordinates intramural and extramural research training, career development, and educational opportunities. The Interagency Oncology Task Force Joint Fellowship Program, an NIH-FDA partnership, supports development of new medical products by training scientists in research-related regulatory review. The Cancer Education and Career Development (R25T) Program supports career development for early career investigators transdisciplinary sciences, producing a generation of researchers cross-trained in disparity research areas and poised to conduct team research. The Calabresi Award in Clinical Oncology (K12) Program brings together clinicians and basic scientists to design and implement hypothesis-based therapeutic trials, promoting translation research findings from bench to beside. The Howard Temin Pathway to Independence Award in Cancer Research (K99/R00) assists early career basic scientists in transitioning from mentorship to independent research by providing funding to complete their fellowships, support their first investigator-initiated research programs, and launch their research careers. The Comparative Molecular Pathology Unit (CMPU) trains translational research investigators by incorporating interdisciplinary education in veterinary medicine with training in human biomedical research. Research Supplements to Promote Diversity in Health-Related Research create the foundation to attract and prepare qualified individuals from underrepresented and underserved populations and individuals with disabilities for careers in cancer research.

→ For more information, see http://www.cancer.gov/cct
→ For more information, see http://ccr.nci.nih.gov/resources/molecular_pathology/training.asp

→ This example also appears in Chapter 2: *Cancer*
→ (E/I) (**NCI**)

Predoctoral Training at the Interface of the Behavioral and Biomedical Sciences: The NIH Institutional Training Grant Program, "Training at the Interface of the Behavioral and Biomedical Sciences," provides an interdisciplinary research training experience and curriculum for predoctoral trainees that integrate both behavioral and biomedical perspectives, approaches, and methodologies. Through coursework, laboratory rotations, and programmatic activities that reinforce training at this interface, the program aims to develop basic behavioral scientists with rigorous training in the biomedical sciences, who are available to assume leadership roles related to the Nation's biomedical, behavioral, and clinical research needs.

→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-06-503.html
→ For more information, see http://www.nigms.nih.gov/News/Results/BehavioralBiomedical070207.htm
→ (E) (**NIGMS**, NCI, NHGRI, NHLBI, NIAID, NIDCD, NIDCR, NINDS)

Informatics Research Training Programs: Exploiting the potential of information technology to augment health care, biomedical research, and education requires investigators who understand biomedicine as well as knowledge representation and decision support. NLM is the principal source of extramural funding for research training in the fields of biomedical informatics, supporting approximately 270 trainees at 18 institutional training programs throughout the country. NLM also provides intramural informatics research training opportunities for another 70 students, postdoctorates, and visiting scientists, as well as training and career development fellowships for health science librarians on the NIH campus and at academic health sciences centers across the country. Collectively, NLM's research training programs encompass health care informatics, bioinformatics, clinical research translational informatics, and public health informatics. Recent highlights and developments in informatics training include:

- A congressional supplemental appropriation for FY 2008 allowed NIH to add 26 NLM training slots.
- A Diversity Short-Term Trainee Program was implemented to improve the diversity of informatics trainees, with funding for 18 trainees at 7 training programs.
- Funds from the American Reinvestment and Recovery Act were committed to support an additional 56 2-year slots at 10 of its informatics training programs.
- A new Clinical Informatics Postdoctoral Fellowship was established to attract young physicians to NIH to pursue research in informatics.

→ For more information, see http://www.nlm.nih.gov/training.html
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (E/I) (**NLM**) (ARRA)

AIDS International Training and Research Program: The AIDS International Training and Research Program (AITRP) began in 1988 as one of the first of a new generation of research training programs sponsored by FIC. This program supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries (LMICs) to conduct multidisciplinary biomedical and behavioral research to address the AIDS epidemic in their countries. This program provides training for scientists from LMIC institutions to strengthen HIV-related research and public health capacities at their institutions. AITRP has trained more than 1,500 trainees. Importantly, several partnerships between AITRP programs and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) were developed in 2008 and 2009. The training provided under the AITRP program targets a cohort of scientists who benefit from the critical thinking and problem-solving skills received through research training. These skills move them forward in their careers into leadership and policymaking positions in public health in their countries. Many PEPFAR programs are directed in-

country by clinician/scientists who have received FIC-supported training. This training, therefore, is an important foundation for the long-term sustainability of the PEPFAR programs. There are many successful partnerships between PEPFAR country teams and FIC AITRP grantees in Zambia, Tanzania, and Cote d'Ivoire.

→ For more information, see http://www.fic.nih.gov/programs/training_grants/aitrp/
→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (E) (**FIC**, NCI, NHLBI, NIAID, NICHD, NIDA, NIMH, OD)

Research Training and Career Development for Veterinarians in Translational Biomedical Research: Two recent reports from the National Academies, *National Need and Priorities for Veterinarians in Biomedical Research* and *Critical Needs for Research in Veterinary Science*, have confirmed the shortage of veterinarians involved in biomedical research. To address the shortage, NIH provides research training awards ("T" Awards) in biomedical research specifically for veterinarians and veterinary students. During FY 2008, more than 75 veterinarians received research training under the "T" mechanism. The mentored Career Development Awards ("K" Awards) to veterinarians serve as a bridge for postdoctoral fellows to become independent investigators. In FY 2008, 22 career development "K" awards were made to young veterinary investigators to increase the number of biomedical researchers with this expertise. Additionally, another initiative encourages the training of veterinarians in nonhuman primate clinical medicine at NIH-supported primate centers to address the shortage of clinical veterinary support for research primate colonies.

→ For more information, see http://www.ncrr.nih.gov/career_development_opportunities/individual_training_grants/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**NCRR**)

Summer Institutes to Train Behavioral, Social and Biomedical Researchers: In addition to its formal research training and career development programs, NIH provides special opportunities for students and investigators to gain hands-on experience in research methodologies particularly relevant to behavioral and social science fields.

- Since 2000, NIH has sponsored the Summer Institute on Design and Conduct of Randomized Clinical Trials (RCTs) Involving Behavioral Interventions. Each year more than 200 applicants compete for 35 fellowships to participate in the 2-week course. Leading researchers and statisticians provide grounding in the principles underlying objective clinical trials; challenges posed by behavioral RCTs; alternative RCT designs; appropriate strategies for enrollment, randomization, and retention of participants; methods for monitoring, coordinating, and conducting RCTs; and strategies for appropriate statistical analyses of RCT data.
- In 2009, NIH initiated an annual Institute on Systems Science and Health, to encourage investigators to make use of modeling and related methodologies to tackle complex problems in behavior and health. The 46 participants in the week-long institute gained a broad overview of systems science methodologies and hands-on training in one of three systems science methodologies (agent-based modeling, system dynamics modeling, or network analysis).

→ For more information, see http://www.chronicdisease.org/i4a/pages/index.cfm?pageid=3851
→ For more information, see http://obssr.od.nih.gov/training_and_education/annual_Health_Services_Research_on_social_work/hsr.aspx
→ For more information, see http://obssr.od.nih.gov/training_and_education/annual_Randomized_Clinical_Trials_course/RCT_info.aspx
→ (O) (**OBSSR**, CDC)

Web-Based Learning Modules for Behavioral and Social Sciences Research: NIH is developing Web-based learning modules to enhance the conduct of behavioral and social sciences (BSS) research related to health. These courses provide interactive learning environments for behavioral, social, and biomedical scientists with the goal of facilitating team-based, multidisciplinary research.

- *Behavioral and Social Sciences Research Interactive Textbook*. NIH is supporting the development of an interactive, online course on research methods and tools for researchers engaging in BSS research on health-related topics. The project aims to demonstrate the potential of BSS research to enhance biomedical research, serve as a resource center for the most current and high-quality BSS research methods, reveal how to obtain authoritative answers to methodological questions easily and efficiently, and identify consistent and rigorous quality standards for the research community.
- *Evidence-Based Behavioral Practice*. Another project established a website and three training modules. A goal of the project is to develop online learning tools to help behavioral practitioners and students integrate research and practice in real-world conditions.
- *Genetics Educational Materials for Behavioral and Social Scientists*: An NIH-supported coalition is creating a Web-based educational program in genetics/genomics for the BSS research community. The program will help train scientists capable of working in interdisciplinary teams to improve our understanding of how interactions among genes, behaviors, and environments contribute to health and disease.

→ For more information, see http://www.ebbp.org/
→ (E, O) (**OBSSR**)

NINR Intramural Training Initiatives: Through a range of initiatives, NINR's intramural program bolsters the Institute's formal extramural research training programs and expedites the development of productive nurse scientists, many of whom also will serve as nursing faculty.

- The Summer Genetics Institute (SGI) is an intense, 2-month, full-time summer research training program for faculty, graduate students, and advanced practice nurses that has been supported annually by NIH since 2000. Hosted by the NINR Division of Intramural Research, the SGI features classroom and laboratory components that are designed to provide a foundation in molecular genetics for use in clinical practice and the research laboratory.
- For recently graduated, doctorally prepared nurse scientists, NIH sponsors the K22 Career Transition Awards, which are designed to facilitate the transition of postdoctoral trainees to independent research careers. Awardees receive up to 3 years of postdoctoral research training in intramural laboratories in Bethesda, Maryland, followed by 2 years of extramural support as they begin tenure-track faculty positions.
- Through its participation in the NIH Graduate Partnerships Program, NINR partners with schools of nursing to provide doctoral students with opportunities for up to 2 years of research training at the NIH. Participating students conduct research under the guidance of an NIH intramural investigator, in areas such as symptom management, genetics, or end-of-life/palliative care.
- Finally, in 2009, NINR and the NIH CC, in association with the Bravewell Collaborative, began offering a 2-year fellowship for research in integrative medicine. The fellowship combines research experiences in the NIH intramural laboratories with instruction through the University of Arizona's Program in Integrative Medicine.

→ For more information, see http://www.ninr.nih.gov/Training/TrainingOpportunitiesIntramural/
→ (I) (**NINR**)

Informatics Training for Global Health: As biomedical information has increased exponentially in recent years, computer-based tools have been developed to access and analyze this information and to aid the process of research design, data management, and data analysis. The sheer volume of data generated in many biomedical and behavioral research projects and in clinical trials can no longer be managed effectively without electronic help. Further, access to computers and the Internet is becoming commonplace in research institutions throughout the developing world. To take

advantage of these tools, individuals with the advanced skills to use them are critically needed. However, despite the central role informatics plays in global health, many low and middle income country (LMIC) institutions have very few informatics experts and a very weak information technology infrastructure. There is a critical need to train local experts who are able to develop local research applications or modify existing platforms to provide tools that are appropriate for the needs, culture, and infrastructure of their institutions and countries. In response, NIH's Informatics Training for Global Health program aims to develop human capital to meet global health challenges, to support the development of research hubs in LMICs, and to bolster the development of expertise in the use of information and communication technologies in support of research and research training.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-09-001.html
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**FIC**, NHGRI, NIBIB, NLM)

Strength from Partnerships

Interdisciplinary Graduate Research Training: A Public-Private Partnership Between NIH and HHMI: Howard Hughes Medical Institute (HHMI) and NIH have developed a joint initiative for Interdisciplinary Graduate Research Training. This innovative public-private partnership, begun in 2005, is intended to facilitate the development of graduate student training in emerging interdisciplinary research environments and to increase the number of interdisciplinary researchers working at the intersection of the biological and physical sciences and/or engineering. Funding for Phase 1 of the initiative was provided by HHMI, which awarded $10 million in 3-year grants to 10 institutions to pilot new and innovative ways to train interdisciplinary scientists. The second phase of this initiative, recently funded by NIH, provides support for graduate student training in interdisciplinary research. The training environments link the educational and research training missions of multiple schools and departments, including biology, chemistry, computational mathematics, engineering, materials science, and physics. They also have many innovative didactic and community-building activities, including "boot camps," team challenges, interdisciplinary courses and laboratories, courses on communication and collaboration, team mentoring, and interdisciplinary rotations, retreats, and seminars.

→ For more information, see http://www.hhmi.org/news/112205.html
→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-08-003.html
→ (E) (**NIBIB**)

Clinical Research Training and Medical Education at the NIH CC: NIH develops, administers, and evaluates clinical research training and medical education initiatives that contribute to the professional growth of the clinical and translational research community, including medical and dental students, physicians in residency and fellowship training programs, established investigators, allied health professionals, and laypersons. The clinical research curriculum is offered at NIH and domestic and international locations. The curriculum consists of the "Introduction to the Principles & Practices of Clinical Research," "Principles of Clinical Pharmacology," and "Ethical & Regulatory Aspects of Clinical Research" courses as well as on-line courses for principal investigators. Extramural researchers have a new opportunity to access the rich training experiences available on the NIH campus via a "Clinical Research Management Sabbatical," which allows clinical investigators to come to the NIH CC to develop the leadership skills needed to create or enhance an optimal environment for conducting clinical research. The NIH CC also has partnered with extramural collaborators and industry to enrich its educational offerings. Via videoconferencing, Duke University School of Medicine offers NIH physicians and dentists an opportunity to receive a Master of Health Sciences in Clinical Research. The Clinical Research Training Program, a partnership supported by NIH and a grant to the Foundation for NIH from Pfizer Inc., trains 30 advanced medical and dental students annually in clinical or translational research.

→ For more information, see http://www.cc.nih.gov/training/index.html
→ (I) (**CC**)

Paul B. Beeson Career Development Awards in Aging Research: The Beeson Awards, co-supported by NIH, the American Federation for Aging Research, and several other philanthropic concerns, offer 3- to 5-year faculty development awards to outstanding junior and mid-career faculty committed to academic careers in aging-related research, training, and practice. Beeson scholars receive funding and resources to pursue their innovative research; protected time for research; mentorship through their own institutions and through the program itself; and extensive networking opportunities. Since their inception in 1995, the Beeson award has provided nearly $80 million to 152 independent investigators, many of whom have gone on to become leaders in the field of aging research.

→ For more information, see http://www.beeson.org
→ (E) (**NIA**)

NIH Training Program Evaluations and Assessments

Annual Assessments of Research Training: Every year, NIH monitors the effectiveness of its research training programs by analyzing the extent to which former Kirschstein-NRSA trainees and fellows remain engaged in biomedical research. Results of these annual assessments routinely have indicated that Kirschstein-NRSA postdoctoral trainees and fellows are more likely to remain active in biomedical research than their peers in the same fields, as indicated by the greater percentage applying for and receiving NIH research support within 10 years of their training.

→ For more information, see http://nihperformance.nih.gov/NR/rdonlyres/9A12CAF4-C39A-4D29-96A4-A57863A6B3A7/12537/FY10OnlinePerformanceAppendixNIHFINAL.pdf
→ (O) (**OER**) (GPRA)

Career Development for Physician-Scientists: NIH supports a number of institutional career development programs for physician-scientists at leading medical institutions across the country. Some of these programs are open to physicians of any specialty, while others are targeted specifically to physicians with particular specialties, such as pediatrics, medical rehabilitation, obstetrics-gynecology, or critical care medicine. NIH has tracked the career progress of physician-scientists who have participated in several of these programs. The results indicated that, depending on the specific program, between 60 and 85 percent of participants subsequently applied for an NIH grant, and between 50 and 75 percent of participants became a principal investigator on an NIH grant. Program participants received funding from all 24 award-granting ICs at NIH. The success rate for subsequent funding varied by the specific program, institution, sex, time since degree, and medical subspecialty. The findings will be used to refine program objectives and to target specific areas for improvement.

→ (O) (**NICHD**)

xTrain: As part of its commitment to electronic research administration, NIH has introduced a system to allow information on participants in institutional research training grants and career development awards to be transmitted to NIH electronically. Through this new system—xTrain, program directors electronically can appoint students and postdoctorates to research training and career development awards and report to NIH when their training is complete. Ultimately, xTrain will replace the paper appointment forms that have been used by NIH training programs since the 1970s and will help NIH manage its research training and career development activities more effectively. Since the introduction of xTrain in June 2008, more than 65 universities have begun using the system. By 2012, all appointments to NIH training grants and institutional career development awards are expected to be made via xTrain.

→ For more information, see http://era.nih.gov/services_for_applicants/other/xTrain.cfm
→ (E) (**OER**) (GPRA)

Evaluation of Extramural Research Training and Career Development Programs at NIAMS: NIAMS conducted an outcome evaluation to assess the success of postdoctoral research trainees who received NIAMS grants and awards through its extramural research training and career development awards program. Like other NIH training and career development grants and awards programs, the NIAMS program is intended to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to biomedical and behavioral research. NIAMS's overall objective is to use a combination of institutional training grants and individual fellowships to ensure a continuing supply of well-trained scientists, prepared to conduct cutting-edge research related to musculoskeletal, skin, and rheumatic diseases. The specific grants and awards that were evaluated are the National Research Service Award (NRSA) institutional training grant (T32), NRSA individual research training grant (F32), and Mentored Career Development Awards (K01 and K08). While NIAMS uses other grant and award mechanisms, these awards were selected both because they represent a high proportion of the total dollars awarded, and because there is sufficient information available about recipients to assess their career progress over time. Overall, a working group of outside experts considered these programs to be successful in maintaining a highly trained workforce, and provided 10 recommendations for consideration. NIAMS has established an internal working group to review each of the recommendations carefully, and several key changes to the program already have been implemented.

→ For more information, see http://www.niams.nih.gov/News_and_Events/Meetings_and_Events/Reports/2007/training_grant_eval_final_report.asp
→ (E) (**NIAMS**)

Investing in the Future: 2008 National Advisory Mental Health Council Workgroup on Research Training: The National Advisory Mental Health Council convened a workgroup, composed of both council members and outside experts, to develop a framework outlining NIMH's research training priorities. The workgroup's goal was to identify the steps needed to develop a workforce equipped with the cutting-edge knowledge, skills, and perspectives that will accelerate the field of mental health research. The training report summarizes important characteristics of the future NIMH research workforce and considers three key issues: the diversity of the workforce; international students and postdoctoral scholars; and researchers holding dual M.D./Ph.D. degrees. The report includes recommendations for the future direction of NIMH-supported research training programs and initiatives, as well as those for program assessment and dissemination to the extramural research community. The report's recommendations were made with the hope that by developing an even stronger mental health research workforce, NIMH will increase the rate of innovative discoveries, and ultimately lead to improved treatment and functioning for people living with mental illness.

→ For more information, see http://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/investing-in-the-future.pdf
→ (E) (**NIMH**)

Review of the International Clinical, Operational, and Health Services Research and Training Award (ICOHRTA): NIH reviewed the first 5 years of the ICOHRTA program. The purpose of the review was to analyze program implementation, identify near-term outputs, and make recommendations for future improvements to the program. Overall, the panel concluded that the program was successful and productive in its first 5 years. Notable accomplishments highlighting the effectiveness of the training program include the following:

- A total of 129 trainees from 18 low- and middle-income countries in 5 world regions have been associated with the program for at least 6 months, and many more individuals have participated in shorter-term training activities.
- Five former ICOHRTA trainees have competed successfully for NIH R01 awards, and one additional trainee is principal investigator on a Cooperative Agreement with the Centers for Disease Control and Prevention. Former trainees also collaborate on at least three NIH awards made to U.S. principal investigators since 2001, including an FIC Trauma award and a Fogerty International Research Collaboration Award.
- A total of 381 peer-reviewed journal articles are known to have been associated with ICOHRTA awards, as are an additional 47 nonpeer reviewed publications such as book chapters, books, and policy documents.
- ICOHRTA played a key role in several important national public health and policy projects.

→ For more information, see http://www.fic.nih.gov/programs/training_grants/icohrta/
→ (E) (**FIC**, NCCAM, NIA, NIDA, NIDCR, NIMH)

Evaluation of NIDDK Research Training Programs: Each year, NIDDK evaluates the 5-, 10-, and 15-year outcomes of individuals who received either Career Development Awards (K awards) or Individual Postdoctoral National Research Service Awards (F32 awards). The most recent evaluation, conducted in 2008, included outcome data from individuals whose grants ended in 1993, 1998, and 2003. A total of 180 former F32 fellows and 139 former K awardees were included in the evaluation. The data showed that 45 to 58 percent (ranges reflect the high and low values of the groups evaluated) of the F32 postdoctoral fellows remained in research at the time of the evaluation. In addition, 50 to 60 percent of the fellows had applied for additional NIH funding; of those who applied, 55 to 68 percent were successful. Among K awardees, 62 to 85 percent remained in research at the time of the evaluation. Furthermore, 71 to 85 percent of the K awardees had applied for further NIH funding, and 75 to 81 percent of those who applied were successful. Data on current funding status and on the number of publications during the last year—and the subsequent 2 years—of the F32 or K award funding also were collected, along with the current position of each awardee, when available. Overall, NIDDK concluded that the trainees have been successful with respect to scientific progress, continuation in research, and applying for funding. NIDDK uses these data to guide its research training programs, which aim to advance research progress through the training of investigators in research relevant to diseases within the Institute's mission. NIDDK also has discussed results of training program evaluations with its Advisory Council for additional input.

→ (O) (**NIDDK**)

Trans-NIH Extramural Career Development Programs

Research Career Development Programs: One of the most challenging transitions in any research career is the progression from postdoctoral trainee to independent scientist. NIH has long used the Research Scientist Development Award (K01) to foster the successful transition of individuals who hold a research or health-professional doctoral degree or equivalent. To support the transition of junior-level clinically-trained investigators, NIH also offers the Mentored Clinical Scientist Development Award (K08) and the Mentored Patient-Oriented Research Career Development Award (K23). For postdoctoral fellows seeking to transition to faculty positions, awards such as the Career Transition Award (K22) and the Pathway to Independence Program (K99/R00) provide mentoring, protected time, and financial support to ease the transition to faculty positions. At the institutional level, NIH offers several Mentored Clinical Scientist Development Awards (K12) that provide support to newly trained clinicians at an institution who are developing their independent research skills and experience. Other specific career development awards are tailored to meet the needs of different research areas and recipients at different career levels.

→ For more information, see http://grants.nih.gov/training/careerdevelopmentawards.htm
→ For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-09-040.html
→ For more information, see http://grants2.nih.gov/grants/guide/pa-files/PA-09-042.html
→ For more information, see http://grants2.nih.gov/grants/guide/pa-files/PA-09-043.html

→ For more information, see http://grants2.nih.gov/grants/guide/pa-files/PA-09-036.html
→ (E) (**OER**)

Building Interdisciplinary Research Careers in Women's Health (BIRCWH): The Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program is an interdisciplinary, mentored, career development initiative that supports junior faculty men and women who are conducting research in women's health. Each scholar has at least two mentors from different disciplines that are part of their interdisciplinary mentoring team. The BIRCWH is co-funded by the NIH Office of the NIH Director, several NIH ICs, and the Agency for Healthcare Research and Quality (AHRQ). To date, 50 BIRCWH programs have been established at 38 institutions and there are currently 26 active BIRCWH sites. More than 378 scholars have participated, of which 79 percent are women. Scholars have published more than 1,300 publications and have successfully competed for 282 NIH research grants. BIRCWH plays a critical role in maintaining the pipeline of junior faculty who are available to conduct women's health research.

→ For more information, see http://orwh.od.nih.gov/interdisciplinary/bircwhmenu.html
→ (E) (**ORWH**, AHRQ, NCI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIEHS, NIMH, ODP/ODS)

Disparities Research and Education Advancing Mission Career Transition Award: This award program facilitates the transition of early-stage investigators working in health disparities or areas that address health disparity conditions and populations from the mentored stage of career development to the independent stage of investigator-initiated health disparities research. The program provides an opportunity for investigators to develop solid research skills during the initial period of up to two years of study and research within the NIH Intramural Research Program. The award may also include a follow-on period of up to three years of salary and mentored research support at the candidate's current institution or organization or an academic or research grantee institution of the candidate's choice. This period of extramural support will facilitate the transition to independence as a researcher in health disparities research.

→ For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-10-001.html
→ (E) (**NCMHD**)

[57] Consistent with Section 487(a)(4) of the PHS Act.
[58] For more information, see http://www.nap.edu/catalog.php?record_id=11275#toc.
[59] For more information, see http://grants.nih.gov/training/career_progress/index.htm.
[60] For more information, see http://grants1.nih.gov/training/NRSA_report_5_16_06-2.doc.
[61] For more information, see http://www.lrp.nih.gov/reports_and_statistics/index.aspx
[62] For more information, see http://www.lrp.nih.gov/pdf/LRP_Evaluation_Report_508final06082009.pdf

Health Communication and Information Campaigns and Clearinghouses

Norma knew she had some of the risk factors for heart disease—high cholesterol, age, and a family history. But it wasn't in her plan to sit around and wait for the worst. "I've had a lot of friends who have had heart attacks, and this has made me aware that I need to take care of myself. You can't wait until a heart attack happens, by then it's too late." So Norma and many other women are grabbing life by the reins and doing what they can to prevent heart disease through a good diet, physical activity, and talking to their doctor about risks and warning signs.

"I try to live a healthy lifestyle by eating healthy foods and finding creative ways to exercise—like dancing," says Norma, who has been touched personally by NIH's Heart Truth®[63] public information campaign. The Heart Truth® message is paired with an arresting visual—the Red Dress®—designed to warn women that heart disease is their number one killer. Since 2002, the Red Dress® has been a powerful symbol to millions of women like Norma who share a common desire to protect their hearts.

Norma and thousands of other residents living in cities with populations at high risk for heart disease continue to benefit from annual Heart Truth Road Show events where they can learn about their personal risk for heart disease and receive educational materials to help them take control of their heart health. By March 2009, 69 percent of women were aware that heart disease is the leading cause of death among women, up from 34 percent in 2000.

Introduction

As the Nation's medical research agency, NIH is a trusted source of information for millions of Americans. Communicating useful health and science information to the American public—a cornerstone of the NIH mission—requires integrative strategies that appeal to NIH's many audiences. The public has many faces: patients, family members, health care providers, scientists, public health workers, voluntary health organizations, policy leaders, and industry. To communicate effectively, NIH uses a variety of strategies and tactics to reach audiences where they are and in culturally competent, accessible ways.

Good communication achieves many goals toward improving health:

- Increasing knowledge and awareness of a health issue, problem, or solution
- Influencing perceptions, beliefs, and attitudes that may change social norms
- Prompting action
- Demonstrating healthy behaviors
- Refuting myths and misconceptions
- Helping forge self-sustainable relationships with communities

Each NIH IC shares a similar set of challenges: translating complex science into useful information and identifying and selecting appropriate communication outlets for key audiences. IC communications teams work directly with intramural and extramural scientists in their mission areas to ensure that the materials they produce are based on the soundest science.

The NIH Office of the Director's Office of Communications and Public Liaison (OCPL) provides an umbrella of leadership and guidance and coordinates communication activities across NIH ICs so the agency provides clear, consistent, and informative materials to the American public. NIH employs a range of strategies to reach Americans, and in particular, the agency continually assesses the most effective and efficient ways to reach those most vulnerable.

Public Information Campaigns and Communications Clearinghouses coordinate the ideas and actions of public and private organizations to reach people where they are. Clearinghouses are resource centers that connect the public with answers to their questions and that work with NIH ICs to develop new resources according to public need. Each year, NIH

distributes nearly 30 million science-based, health information publications to requestors who rely on NIH and its news stories, press releases, and publications for authoritative information. Information campaigns often package and deliver multiple communication products with the goal of either provoking a specific action or bringing about a behavioral change. NIH-sponsored health campaigns provide current, comprehensive, science-based information about the symptoms, diagnosis, and treatment of various diseases and conditions, often helping individuals to play a greater role in improving their health.

Each year, NIH distributes nearly 30 million science-based, health information publications to requestors.

Innovative Uses of Social Media that keep pace with modern technology enable NIH to connect with young and mobile audiences who rely nearly exclusively on electronic means of communication. Engaging and informative online resources—blogs, pod- and vodcasts, YouTube, wikis, and others—are powerful communication tools that NIH is using to reach crucial target audiences. NIH has created a presence with its portal for vodcasts and videos. NIH Vodcast episodes and the "NIH4Health" channel on YouTube reach millions of users each month.

Reliable, Authoritative, Accessible, Science-Based Health Information for a range of age groups is readily available online at the NIH health information portal. All NIH ICs continuously contribute scientifically vetted materials to this site, including information in easy-to-read formats and in languages other than English.

Cooperative Interactions with the Media enable NIH to provide the press with access to scientific and health expertise and a vehicle to tell health and science stories. In turn, programs that teach media literacy help impressionable youth deconstruct media messages so they can identify a sponsor's motives. Companion strategies guide communicators in composing messages attuned to the intended audience's point of view.

Partnerships with Outside Organizations help NIH achieve its mission to share and translate the results of medical research. Partnering activities also may include seeking entertainment industry support for a health issue. NIH routinely and freely shares materials with public health organizations, advocacy groups, schools, and community health officials, and encourages the personalization of health information based on individual and community needs.

Public Participation is a key part of NIH's ability to carry out its mission. NIH employs a multifaceted approach to public engagement and outreach. One approach is through the NIH Director's Council of Public Representatives (COPR)—a Federal Advisory Committee composed of up to 21 members of the public who provide the public's perspective into the NIH research priority-setting process as well as the agency's public health education and public engagement efforts. Through COPR, the agency connects directly with the public at the level of the NIH Director. The Council serves as the public's voice on issues relating to the NIH mission, informs the public of the research and health benefits gained through the public's investment in NIH, and helps NIH understand the public perspective and engage the public in NIH activities. Members of this group represent a wide variety of backgrounds based on geographic location, race, ethnicity, and experience, including patients, family members of patients, health care professionals, scientists, health and science communicators, and educators.

NIH's Council of Public Representatives serves as the public's voice on issues relating to the NIH mission, informs the public of the research and health benefits gained through the public's investment in NIH, and helps NIH understand the public perspective and engage the public in NIH activities.

NIH's "Clear Communication" effort builds upon sound research results provided by trans-NIH programs and activities. With this program, NIH aims to cultivate and contribute to a growing health literacy movement by increasing sharing of information including NIH educational products and research, lessons learned, and research in the area of health literacy. The program provides accessible materials and resources to help professionals reach individuals with literacy challenges,

as well as guidelines on how to create such materials. Sections on the Clear Communication website are devoted to health literacy, plain language, cultural competence, and NIH-funded health literacy research.

On a larger scale, NIH health communication programs move people from awareness to behavior change and are aimed at the societal level. Efforts to reduce drunk driving, for example, have changed individual and societal attitudes, behaviors, and policies through multiple forms of intervention, including communication. Groups with defined structures, such as associations, clubs, or civic groups, are important vehicles for carrying health messages and for creating and sustaining policy changes at the local level.

NIH also works diligently to develop and deliver transparent and timely information about funding practices and policies to ensure that the engine of medical research discovery runs at top speed and that the scientific workforce's information needs are met. NIH communicates regularly with the scientific community, including grantees, industry, and the scientific and academic press, to give them the sources and tools they need to access the latest research results and information.

Catalogs of Health Communication and Information Campaigns & Clearinghouses Activities

In response to the mandate under SEC. 403 (a)(4)(C)(ii) of the of the Public Health Service Act to provide a catalog of information clearinghouses, included here is a live link to a website featuring NIH's information clearinghouses. In response to the mandate under SEC. 403 (a)(4)(C)(iii) to provide a catalog of public education and information campaigns included here is a live link to a website featuring NIH's Education and Awareness Campaigns.

Summary of NIH Activities

NIH ICs are congressionally mandated to provide science-based health information to the public. As science and society change, the mode of information exchange needs to change, too. Near instant access to information through electronic media creates a new role for Federal agencies—trusted sources of credible information—to serve as a gateway for clear and balanced information about science and medicine, in a range of accessible formats.

New knowledge of human biology and advances in technology has given scientists the ability to better understand the language of human genes. This has thrust modern society into an age in which personalized medicine is nearing reality. That means that the results of modern scientific research are beginning to tell us how particular individuals will react to a medicine or a chemical in the environment, as well as which health problems they may be prone to. Having this individualized health information and understanding the role of cultural influences will enable Americans to implement prevention measures against a range of diseases and conditions.

A key aspect of the departure from "one-size-fits-most" medical care is individual involvement in health care and decision-making. Engaging the public in its own health is a crucial step toward achieving prevention-based medicine.

Delivering Health Information and Science News to the Public

Keeping the public informed about new developments in NIH-supported medical research is a primary goal of NIH health communication efforts. A variety of scientifically vetted, general health information and science news resources are available through NIH, including:

- *NIH Research Matters*, an e-column offering a glimpse into research accomplishments of NIH and NIH-funded scientists using brief, accessible stories that describe research results and put them in perspective
- "Research Results for the Public," a site that provides disease-by-disease descriptions of research progress and an interactive map of NIH research funding across the Nation
- "NIH & Clinical Research," a health information site that features podcasts, vodcasts, and radio programs in English and Spanish on clinical research
- *NIH News in Health*, a newsletter and online resource that provides practical and accessible health information monthly to public health workers, community centers, aging centers, voluntary health organizations, physicians, and hospitals

- "Talking to Your Doctor," a site that offers NIH-produced resources from several ICs to enable patients to play an active role in their health care
- "The Women's Health Resources Web Portal," a site created to promote awareness and facilitation of research on women's health by providing Web-based resources, including access to scientific literature and research reports, clinical trials opportunities, and consumer health information pertaining to women's health

Because the press is a major source of health information for the public, NIH staff members work every day to provide background for media sources and identify key knowledgeable scientists to help reporters develop their stories. OCPL is the central coordinator and responder for media relations at NIH. In addition, to help the press interpret medical information with greater ease and accuracy, NIH also offers a highly acclaimed, free annual training course, "Medicine in the Media," now in its eighth year.

NIH also has developed a network of public information officers (PIOs) at academic institutions nationwide to ease communication, encourage collaboration, and coordinate publicity between NIH PIOs and communications staff at NIH-funded grantee and contracted institutions.

In our Internet-driven society, the Web and related media are indispensible sources of news. Recent research has shown that a majority of Americans who request NIH information not only use it, but also share it with others. More than 40 percent who use Web materials related to health take that information with them to their physicians' offices. The NIH homepage, developed and managed by OCPL's Online Information Branch, serves as entry point to the hundreds of individual NIH websites that comprise the NIH community of online programs, services, and information spanning thousands of health topics and research activities. One important page on the NIH website is "Get Involved at NIH" at http://getinvolved.nih.gov/, which serves as the NIH gateway for public participation, input, and feedback. Combined, the NIH websites, including those run by NLM, whose basic mission is to improve the dissemination of biomedical and health information, are accessed more than 3 billion times each year.

NIH and the Wikipedia Foundation are working together to make health and science information more accessible and reliable to the widest audiences possible.

In July 2009, NIH joined forces with the Wikimedia Foundation, the nonprofit, collaborative arm of Wikipedia®. Wikipedia is the international online encyclopedia that is the fourth largest Internet property. It attracts approximately 65 million visitors monthly and has information in 270 languages. NIH and Wikipedia are working together to make health and science information more accessible and reliable to the widest audiences possible. This historic "Academy" collaboration is the first of its kind for both organizations. NIH subject matter experts will contribute to Wikipedia and also help develop best practices for future sessions. Guidelines about how to contribute are available on the NIH website for scientists across the country. In addition, NIH communication offices have piloted use of social media for the past few years and will now implement newly released HHS social media guidelines to increase reach and to meet the audience where they are with added transparency and efficiency.

"i on NIH" is an Internet-based video program designed to educate and inform anyone interested in health-research news. For 30 minutes, once a month, i on NIH conveys the excitement of advances and important discoveries in medical research in a news-magazine style.

NIH Radio posts new stories each week to provide radio stations and the public with the latest information about NIH research findings, highlights of press conferences, and health campaigns. The NIH Radio News Service, now more than 20 years old, is available to millions of listeners on satellite radio through a feature called "NIH Health Matters," a 60-second spot aired on the HealthStar Radio Network and nearly 1,000 radio stations nationwide, including overnight airing on Washington, D.C.'s WTOP.

- "NIH Research Radio" is a biweekly podcast that can be listened to on a computer or downloaded into individual portable MP3 players.

To address the needs of those seeking more specific information about various diseases and conditions, NIH ICs produce a wide spectrum of more tailored science and health information in various formats, including the following selected examples:

- "Healthy Moments" is a radio series that provides tips to prevent and control diabetes, kidney disease, and related health disorders. The reports air on RadioOne's Majic 102.3 FM and two additional RadioOne, Inc. radio stations.
- The NIAMS Information Clearinghouse and the NIH Osteoporosis and Related Bone Diseases National Resource Center[64] produce and distribute health education materials in a variety of languages and formats on diseases and conditions of bones, joints, muscles, and skin to patients, health professionals, scientists, voluntary and professional organizations, and the media.
- NIH hosts online Picture and Video Galleries that showcase NIH-supported research results in vivid color and in motion. The images and videos illustrate various cutting-edge concepts in modern biomedicine and have been requested for use by *Discover* magazine and several textbook publishers.
- An annual "Medicine for the Public" lecture series has been presented every fall since 1978. The series provides the public with information on medical research geared in a lay-friendly format. The lectures are free and span a wide range of topics such as cancer screening, mental health, asthma, and many others.
- Various NIH ICs take advantage of commemorative days—for example, National HIV/AIDS Awareness Day—to publicize the importance of pressing health issues. Announcements from top NIH leadership are picked up by the media and highlight dozens of health diseases and disorders that affect the American public, offering timely opportunities and suggestions for prevention and treatment.
- In FYs 2008 and 2009, NIH added nearly 1.4 million articles from the biomedical journal literature to PubMed/MEDLINE, a vital tool for biomedical research, clinical medicine, and consumer health. The Indexing 2015 initiative is pursuing increases in the speed and efficiency of indexing through natural language processing and other automated techniques.

Reaching Different Audiences

On January 21, 2009, President Obama issued a directive to all Federal agencies calling for greater transparency, public participation, and collaboration. In response to this directive, and in keeping with the work that has already been done by NIH to encourage public input and provide the public with science-based health information and knowledge about the science it conducts and supports, the agency posted a Request for Information (RFI) to offer a new public input opportunity. NIH received an unprecedented response from both individual organizations and members of the public and will work with the results to enhance health information. Information gathered will help NIH develop and disseminate health, medical, and scientific information to a wider variety of audiences.

The agency anticipates using new outreach strategies and tools, including community-level outlets and Internet-based social media, to connect with the diverse American public that includes patients, families, friends, scientists, health professionals, public health workers, industry, health care providers, congressional staff, and voluntary organizations.

As America continues to diversify, NIH continues to gather input from communities and groups on cultural factors. This information is essential for the development of high-quality, tailored health information. Individuals and communities require culturally appropriate information on specific health conditions or concerns, and NIH ICs work hard to develop quality products to meet this need. For example, NIH harbors a special responsibility to serve America’s youth through targeted approaches that address the needs and wants of modern children and teens. Four examples of how NIH is meeting the information requirements of specific audiences are:

- The NIH website continues to incorporate new technologies, including customized streaming news feeds such as Really Simple Syndication (RSS), Podcasting and Vodcasting, and health video posted on NIH’s Facebook page,

YouTube, and Twitter sites, to reach the tech savvy segment of the population whose favored modes of communication are social media.

- *Control del dolor: Apoyo para las personas con cáncer* (*Pain Control: Support for People with Cancer*) are booklets produced in Spanish and English to address the needs of those suffering from cancer pain. They provide culturally sensitive information on cancer medicines and side effects, communication, pain control methods, and coping methods for the physical and emotional effects of pain.
- Four sets of heart health booklets offer motivation and action steps to incorporate heart healthy behaviors into daily life for Latino Americans and Filipino Americans. The booklets include references to culturally appropriate foods, activities, and situations.
- The NIH *MedlinePlus* magazine, and its bilingual Spanish counterpart *NIH Medline Plus Salud*, are quarterly consumer magazines focused on bringing the latest clinical findings to patients and their families. The magazines are complementary to the MedlinePlus and MedlinePlus en español websites, and are distributed to the public via doctors' offices nationwide.

The NIH website continues to incorporate new technologies, including customized streaming news feeds such as Really Simple Syndication (RSS), Podcasting and Vodcasting, and health video posted on NIH Facebook, YouTube, and Twitter sites.

NIH also keeps tabs on the health information needs of population groups that need specialized information, and NIH ICs proactively develop tailored communications products and approaches. These include science-based fact sheets, checklist resources, public service announcements, K-12 educational materials, and more, such as:

- In 2007 the Trans-NIH American Indian and Alaska Native Health Communications & Information Work Group, with representation from 16 NIH ICs, began working with the Indian Health Service's National Community Health Representative Program on activities of mutual interest. To help increase awareness of the vast array of resources provided by the NIH, the Work Group sends quarterly mailings of health information to a network of 1,600 Tribal community health representatives nationwide who serve as lay health educators and patient liaisons in Native communities.
- Since 2006, NIH, in collaboration with the Coalition for Imaging and Bioengineering Research, has hosted several campus tours each year aimed at introducing congressional staffers and patient advocacy group members to the cutting-edge research programs and laboratory facilities of NIH.
- Fifteen NIH ICs collaborated to develop the 43 health topics included on the popular www.NIHSeniorHealth.gov website, which covers health topics of particular interest to older adults such as Alzheimer's disease, cataracts, shingles, exercise, nutrition, fall prevention, taking medicines, and Medicare basics—all in a clear, easy-to-read format.
- Because African Americans are at high risk for developing heritable kidney disease, NIH developed and promoted *The Family Reunion Health Guide* for use at African American family reunions. This resource has everything African American families need to talk about the connection between diabetes, high blood pressure, and kidney disease.

NIH also is engaged in sustained NIH media and multicultural outreach efforts. Staff members produce 4 radio programs, including Spanish language programming, that feature public service announcements, 60-second reports, and long-format interviews. NIH also produces the award-winning podcast series "Pinn Point on Women's Health." The series highlights topics in women's health research through conversations with NIH experts on a variety of subjects, and breaking news on women's health research in a segment titled "Hot Flashes."

Rapidly Responding to Time-Sensitive Issues

New challenges arise constantly in our fast-paced world. Often, health communications need to be developed swiftly to raise awareness or encourage people to take urgent and specific actions based on a new finding or a health threat. In developing its communications programs, NIH remains vigilant to the need for timely communications materials. The following are selected examples from across NIH.

In 2009, a virus with clear pandemic potential, the 2009 H1N1 influenza virus, emerged. Because the scientific and public health communities had expected this scenario, NIH and HHS were poised to work collaboratively with other Federal agencies to prepare for a possible epidemic. In addition to a range of scientific and public health measures, NIH teamed with the U.S. Centers for Disease Control and Prevention (CDC) to provide consistent messaging in a coordinated and timely fashion for health consumers wanting the most up-to-date facts and guidelines about the 2009 H1N1 epidemic.

OCPL provides ongoing strategic and tactical advice on time-sensitive issues. The office works with NIH leadership, both in the OD and across NIH ICs, to ensure coherent, responsive messages. In 2009, OCPL was the focal point at NIH for communicating the impact of the American Recovery and Reinvestment Act (ARRA) by identifying and publicizing plans and funding opportunities. OCPL has been closely involved with the development of NIH processes for the agency's ARRA communication efforts.

Recognizing Problems and Taking Action

National data point to a serious crisis in that currently available health information is too difficult for average Americans to use to make health decisions.[65] The first ever National Assessment of Adult Literacy[66] determined that only 12 percent of U.S. adults had proficient health literacy, and more than a third of U.S. adults—77 million people—would have difficulty with common health tasks, such as following directions on a prescription drug label or adhering to a childhood immunization schedule using a standard chart.

The HHS Healthy People 2010 initiative established improving health literacy as a national health objective. Following the April 2004 Institute of Medicine report, *Health Literacy: A Prescription to End Confusion*, NIH issued a series of program announcements to encourage empirical research on health literacy concepts, theory, and interventions as they relate to public health priorities identified in Healthy People 2010.

A growing research base[67] is investigating how advances in knowledge about health literacy can inform intervention strategies and have an impact on quality of life and on the reduction of health disparities in general and special populations. Various approaches to addressing this vexing problem currently are underway, such as:

- Determining the effect of low-income parents' literacy levels on safety information comprehension and adoption of behaviors to prevent child injury
- Testing a literacy-focused program that provides educational assistance from pharmacists at the time of hospital discharge to people hospitalized with heart problems
- Identifying the spectrum of medical errors and adverse drug events in the elderly and how literacy affects medication safety
- Evaluating the relationship between informed consent, health literacy, and the documents and tools used to communicate with those who might participate in research studies
- Testing the effectiveness of a clinic-based health literacy intervention to improve initial and repeat use of colorectal and breast cancer screening in rural areas

An important component of solving health-related problems is identifying and understanding the context in which gaps in knowledge and communication arise and persist. For example, many dentists do not feel sufficiently trained to provide services to people with special needs. To help increase access to dental care, NIH developed a series of publications to equip general dentists and dental hygienists with information they need to deliver quality oral care to people with developmental disabilities.

A 2006 survey completed by NIH and the American Association of Retired People (AARP) revealed that nearly two-thirds of adults older than age 50 use complementary and alternative medicine, but only one-third of them share that information with their physicians—creating the potential for serious complications. NIH launched a new patient/provider education initiative, Time to Talk, which encourages open discussion of all health care practices to ensure safe and coordinated care.

Although the life expectancy of the American people has reached a historic high, along with it has come an increase in the number of people living with, and dying from, chronic debilitating diseases. By communicating to the public and the media the results of its important research in this area, NIH provides timely and helpful information to family members and loved ones of the dying.

By communicating to the public and the media the results of its important research on end-of-life, NIH provides timely and helpful information to family members and loved ones of the dying.

Rethinking Drinking, a new website and downloadable booklet, aims to help many people reduce their risk for alcohol problems, a serious societal issue. The new materials present evidence-based information about risky drinking patterns, the alcohol content of drinks, the signs of an alcohol problem, along with information about medications and other resources to help people who choose to cut back or quit drinking.

As the American population ages, the Nation's disease burden is shifting toward conditions that affect older people. Building on the success of an earlier award-winning partnership with Home Box Office (HBO), in 2009, NIH and HBO copresented the multiplatform public health series, "The Alzheimer's Project," to help widen public understanding of this disease that affects millions of people and their caregivers.

In 2009, NIA and HBO co-presented the multi-platform public health series, The Alzheimer's Project, to help widen public understanding of this disease that affects millions of people and their caregivers.

Many urgent health issues continue to remain "under the radar," unduly affecting vulnerable groups. For example, chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States. NIH developed the COPD: Learn More Breathe Better® Campaign, which encourages people at risk to get a simple breathing test and talk to their doctors about treatment options.

Partnering With Outside Organizations

NIH ICs receive regular input from a wide range of outside organizations, and when appropriate, engage in strategic partnerships and collaborations that can enhance NIH's ability to carry out its mission as the Nation's medical research agency. Partners include nonprofit groups, such as voluntary health agencies and community-based organizations. These groups can increase the reach of NIH health communications and outreach programs. Agency interactions with such groups range from routine meetings to the establishment of novel programmatic initiatives and partnerships that can include co-funding of research. These efforts are an important way for NIH to receive regular input from its public constituencies and to forward research announcements, research results, agency news, and scientific press releases.

Examples of projects involving NIH ICs and non-profit organizations include:

- NCI's Community Networks Program, which is designed to reach communities and populations that experience a disproportionate share of the cancer burden. These include African Americans, American Indians/Alaska Natives, Hawaiian Natives and other Pacific Islanders, Asians, Hispanics/Latinos, and underserved rural populations. Strategic partnerships and collaborations enhance vital training, research, and educational functions of this program.
- NIMH's Outreach Partnership Program, which joins with national and state organizations to bridge the gap between research and clinical practice. The program helps disseminate the latest scientific findings; inform the public about mental disorders, alcoholism, and drug addiction; and reduce the stigma and discrimination associated with these illnesses. NIMH has established a formal process to ensure consistent, open dialogue with its major stakeholders through regularly scheduled meetings between their representatives and the NIMH Director and senior staff.
- The NIAMS Health Partnership Program, a community-based, collaborative research program between NIAMS and Washington, D.C., area community organizations. Through research with underrepresented patients affected by arthritis and other rheumatic diseases, the program studies health disparities and their causes and provides direction for improving the health status and outcomes of affected minority communities. Its Community Health Center,

located in the Columbia Heights area of northwest Washington, D.C., gives the community access to specialized care and health information, and provides NIH researchers with access to patients most affected by rheumatic diseases.
- NIEHS's Partnership for Environmental Public Health, which brings together scientists, community members, educators, health care providers, public health officials, and policy makers. A hallmark of this program is that communities are actively engaged in all stages of the research, dissemination, and evaluation. This ensures that vital information about linkages between exposures and disease can be discovered and used to promote health and reduce the risk of disease across the populations at highest risk.
- The NIDCR-hosted annual Patient Advocates Forum, which brings together voluntary health organizations with a shared interest in the oral health effects of their respective disorders and conditions. Begun in 2000, the forum provides an opportunity for NIH to solicit input from the public on a range of NIDCR activities and policies, and to keep the advocacy groups informed about ongoing and planned research programs of particular interest to their constituencies.

Where appropriate, NIH ICs partner with the private sector to reach target audiences and achieve agency health communication goals. Examples of projects involving NIH ICs and the private sector include:

- The NEI Health Education Program Partnership, which consists of more than 70 public and private national organizations interested in eye health education. The purpose of the partnership is to establish ongoing, interactive, mutually beneficial relationships with the NEI and other organizations to facilitate collaboration; to exchange information, views, and materials on eye health education; and to identify and target audiences at higher risk of eye diseases and conditions.
- The Bethesda Hospitals' Emergency Preparedness Partnership, a unique team of emergency responders from Federal, military, and private health care agencies. This partnership joins the NLM with three hospitals in close proximity—the NIH CC, the National Naval Medical Center, and Suburban Hospital—to integrate and leverage resources for local, regional, or national emergencies. Among the group's activities are periodic disaster drills.
- The National Diabetes Education Program, which is co-led by the NIDDK and CDC, works with more than 200 partners at the Federal, State, and local levels to improve the treatment and outcomes for people with diabetes, promote early diagnosis, and prevent or delay the onset of type 2 diabetes. Partners include professional associations, national service and civic organizations, and community groups.

Outreach to the Scientific and Research Communities

In addition to communicating science and health news and information to the public, NIH reaches out to the scientific and research communities to share information and obtain input. Many of these communications campaigns are essential elements in the development of science policies that fit the needs of the NIH audiences that extend beyond researchers to include patients and advocacy groups that are vital participants in the research enterprise. For example, through one recent outreach effort, NIH obtained critical input that informed the agency's issuance of the NIH Stem Cell Guidelines in July 2009.

In addition to communicating science and health news and information to the public, NIH reaches out to the scientific and research communities to share information and obtain input.

In other outreach activities, NIH developed and disseminated timely information about several pressing issues relevant to the scientific community, such as enhancements to the peer review process and new opportunities and requirements resulting from implementation of ARRA.

NIH continues to partner with the ResearchChannel consortium, a public service organization that broadcasts the latest research information free-of-charge, 24 hours per day through satellite and cable television systems—providing access to more than 30 million U.S. subscribers. Much like C-Span communicates political developments to a broad public audience, the ResearchChannel provides wall-to-wall coverage through DIRECTV of nothing but research. The channel also is available on 70 university and school-based cable systems in the United States and overseas.

NIH leads by example in addressing scientific workforce-related issues, and communication about these problems is a key element toward finding tractable solutions. In December 2008, NIH hosted the largest national conference ever on health

disparities—the first summit of its kind that involved all NIH ICs and brought together more than 4,000 national and international clinicians, researchers, policy leaders, academicians, and community leaders. The conference spurred new lines of communication among researchers, spanning a broad range of fields and strategies related to combating health disparities and addressing the companion problem of low health literacy.

Following the release of the National Academies report, *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, NIH created a Working Group on Women in Biomedical Careers. Co-chaired by the NIH Director and ORWH Director, the group is currently working to address recommendations from two conferences held on the topic: "The National Leadership Workshop on Mentoring Women in Biomedical Careers," and "Women in Biomedical Research: Best Practices for Sustaining Career Success." NIH continues to spread the word about the meeting proceedings and their impact on the broader scientific community.

As a world health leader, NIH also must extend its reach to the international scientific community. NIH develops new partnerships among U.S. scientists, institutions, and counterparts abroad to advance research and training in the biomedical and behavioral sciences. The partnering activities foster communications about health and research needs and thus identify opportunities for collaboration with foreign science-funding agencies, the U.S. Department of State, U.S. technical agencies, and international organizations.

Several ICs have developed focused communications tools to provide assistance to, and enable bidirectional communication with, the scientific community and grantees in particular, such as:

- In 2009, NIGMS changed its *Feedback Loop* electronic newsletter, which had been published 3 times a year since 2005, into a blog that posts news and other information as it happens. Site users can submit comments and ask questions, which Institute staff answer. This interactive approach has been especially helpful in communicating time-sensitive information about ARRA.
- The “NCRR e-Reporter” fosters communication, collaboration and resource sharing in areas of current interest to scientists and the public. More than 2,400 subscribers include NCRR grantees, as well as other stakeholders in research, such as leaders in academia, industry, voluntary health organizations, patient advocacy groups, scientific professional societies, policy makers, and science teachers.
- The “NEI Pipeline” is an e-mail broadcast service intended to keep the vision research community informed of grant opportunities, new initiatives, and other newsworthy information concerning NEI and NIH.
- "NIH Grant Cycle: Application to Renewal," produced by NIAID, is an online tutorial that combines graphics and text to explain how to successfully compete for an NIH grant. A reinvention of NIAID’s "All About Grants" tutorials, the new resource divides the funding lifecycle into 12 phases and offers stage-specific information and advice for scientific investigators.
- OCPL developed a constituency database, which contains approximately 400 contacts for advocacy organizations, colleges and universities, hospitals and research centers, and professional societies. Approximately 10 to 12 emails are distributed to this list annually, on topics such as the NIH Peer Review Enhancement Effort; the Research, Condition, and Disease Categorization system; Public Access Policy; and relevant scientific meetings.

Conclusion

In this exciting and quickly evolving era of modern science, NIH has the responsibility—and the privilege—of finding novel ways to connect with the American public. This challenge goes beyond unidirectional delivery of health-related materials, since education involves much more than understanding information. Rather, this urgent task invites a dialogue with the general public, scientists, health care providers, and policy makers to assess what people know, what they want to know, and how to meet those needs of varied audiences. Bringing science to life through innovative materials and programs is a proud tradition of NIH. Thus, NIH continues to employ a wide variety of communication vehicles and makes information available through cutting-edge and audience-tested outlets and strategies.

Clear, yet savvy, health communication approaches are paramount to helping people take advantage of research advances to improve their health.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Delivering Health Information and Science News to the Public

Disseminating Evidence-Based Health Information on Diabetes and Digestive and Kidney Diseases: The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) were created to disseminate evidence-based educational materials on diabetes and kidney disease, respectively. For example, the NDEP encourages people to take "small steps" to prevent type 2 diabetes. The NDEP also promotes the importance of comprehensive diabetes control in its Control Your Diabetes. For Life educational campaign. The NKDEP encourages African American families to discuss kidney disease at family reunions, and also provides tools and resources for health care providers to help coordinate care and improve patient outcomes for kidney disease. Both programs tailor materials for minority groups at high risk. Information Clearinghouses also provide key health information for patients, health care professionals, and the general public. A recent campaign highlighted the importance of using accurate methods to test hemoglobin A1c in people with diabetes who have sickle cell trait or other inherited hemoglobin variants. Other recent campaigns raised awareness of celiac disease and interstitial cystitis. The Weight-Control Information Network provides up-to-date, science-based information on weight control, obesity, physical activity, and related nutritional issues.

→ For more information, see http://www2.niddk.nih.gov/HealthEducation/
→ For more information, see http://ndep.nih.gov/
→ For more information, see http://nkdep.nih.gov/
→ For more information, see http://win.niddk.nih.gov/
→ This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
→ (E) (**NIDDK**, CDC)

New Publications on Mental Health Disorders: NIH has developed several new mental health publications, including booklets and fact sheets on attention deficit hyperactivity disorder, panic disorder, obsessive compulsive disorder, bipolar disorder, bipolar disorder in children and teens, post-traumatic stress disorder, anxiety disorders, mental health medications, and a participants' guide to mental health research. Several of the publications also are available in Spanish and easy-to-read versions.

→ For more information, see http://www.nimh.nih.gov/health/publications/index.shtml
→ (O) (**NIMH**)

NIDCD Information Clearinghouse: NIDCD's Information Clearinghouse disseminates free health information in the areas of hearing, balance, smell, taste, voice, speech, and language to inquiring members of the public. For the years 2008-2009, the NIDCD Information Clearinghouse has maintained a toll-free phone and TTY number for the public and has ensured that NIDCD publications remain current and timely by adding or updating bilingual fact sheets and other

educational materials for dissemination to the public. On average, the clearinghouse distributes 250,000 materials each year. In addition, the clearinghouse disseminates NIDCD health information materials at more than 28 professional conferences and health fairs around the country. Clearinghouse staff also have assisted in the planning and implementation of NIDCD's new campaign against noise-induced hearing loss, It's a Noisy Planet. Protect Their Hearing.

→ For more information, see http://www.nidcd.nih.gov/health/
→ (O) (**NIDCD**)

The Genetic and Rare Diseases Information Center (GARD): Since 1989, repeated studies and panels found that patients and families, as well as physicians, had great difficulties obtaining needed information about the almost 7,000 rare diseases known today. Then NIH established GARD. Since its inception more than 7 years ago, the information center has provided approximately 24,102 individualized responses about 6,497 different rare and/or genetic diseases. On January 30, 2008, GARD introduced new online information resources about rare and/or genetic diseases on the ORDR website for the public. Now, when a person submits a question to GARD about a particular condition, the question is edited and de-identified to ensure confidentiality and posted with its answer to the disease webpage on the ORDR website. A list of resources also is added to each disease webpage for additional information. Information specialists remain available to assist users directly and answer questions in both English and Spanish by telephone, e-mail, mail, or TTY. In the first year, visits to the webpages quadrupled from an average of 500 visits to 2,000 visits per month and continue to increase steadily. Given that the number of visitors and visits to the webpages continues to increase, with more than 250,000 additional individuals using the services of the information center, the sustained lower direct inquiry volume suggests that people are finding answers to their questions on the new Web disease pages without requiring the personal assistance of information specialists.

→ For more information, see http://rarediseases.info.nih.gov/GARD/
→ For more information, see http://rarediseases.info.nih.gov/
→ (O) (**ODP/ORDR**, NHGRI)

Genetics Home Reference (GHR) and GeneTests: GHR is an online resource created for the general public that provides basic information about genetic conditions and the genes and chromosomes related to those conditions. In FYs 2008 and 2009, the system was expanded to include information on 200 more genetic conditions and 200 more genes. The website now covers more than 400 genetic conditions, more than 600 genes, all the human chromosomes, and information about disorders caused by mutations in mitochondrial DNA. GHR also links to GeneTests, a resource developed for health care professionals that provides current, authoritative information on genetic testing and is used in diagnosis, management, and genetic counseling. In addition to peer-reviewed disease descriptions, GeneTests includes voluntary listings of laboratories offering in-house testing and clinics providing genetic evaluation and genetic counseling. GeneTests is designed to promote the appropriate use of genetic services in patient care and personal decision making.

→ For more information, see http://ghr.nlm.nih.gov
→ For more information, see http://www.ncbi.nlm.nih.gov/sites/genetests
→ (I) (**NLM, NHGRI**)

Exhibitions for the Public: NIH continues to present lively and informative exhibitions that enhance the awareness and appreciation of science, medicine, and history. *Visible Proofs: Forensic Views of the Body* closed in February 2008 after a highly successful 2-year run. A new exhibition, *Against the Odds: Making a Difference in Global Health*, which looks at the revolution in global health that is taking place in towns and cities around the world, opened in FY 2008 and will continue through FY 2010. An exhibit titled *Harry Potter's World: Renaissance Science, Magic, and Medicine* also opened in 2008. Using historical materials from the NIH, this exhibition explores Harry Potter's world and its roots in Renaissance magic, science, and medicine. Scores of school groups and other organizations visit the exhibitions each year, and many more are able to access the accompanying online versions. Through a Traveling Exhibitions program, traveling

versions of the exhibits also are made available to libraries across the Nation after they close at NIH, with six exhibits currently included in this program.

→ For more information, see http://www.nlm.nih.gov/hmd/about/exhibition/
→ (I) (**NLM**)

Linking Research Advances to NIH Funding: NIGMS publishes a monthly electronic newsletter, *Biomedical Beat*, that highlights recent research advances made by grantees and features cool scientific images. Through this and other activities, the Institute works to make connections between NIH grant funding and research advances by scientists at universities, medical schools, and other institutions.

→ For more information, see http://publications.nigms.nih.gov/biobeat
→ (O) (**NIGMS**)

MedlinePlus and MedlinePlus En Espanol: MedlinePlus and the Spanish language MedlinePlus En Espanol provide access to high-quality consumer health information on more than 800 diseases and conditions, with authoritative information from NIH, other government agencies, and health-related organizations. Enhancements in FYs 2008-2009 included improved search capabilities and addition of summary information. Content also was expanded to include information in more than 40 languages, addressing the growing needs of non-English-speaking patients. Go Local links from MedlinePlus, developed in partnership with libraries across the country, enable users to find relevant health services in local geographic areas. The number of Go Local sites increased to 34 in FY 2009, covering 46 percent of the U.S. population. The *NIH MedlinePlus Magazine* transmits the latest useful research findings in lay language, with feature stories on topics such as colorectal cancer, post-traumatic stress disorder, and childhood diseases. More than 600,000 copies of the magazine were distributed free to physician offices in FY 2009, up from 50,000 in FY 2006. In addition, a Spanish language edition, *Salud!*, was launched in FY 2009, as were online versions of both English and Spanish language magazines.

→ For more information, see http://www.medlineplus.gov
→ For more information, see http://medlineplus.gov/spanish
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (I) (**NLM**)

Reaching Different Audiences

Education and Outreach: NCI's Office of Communications and Education (OCE) provides comprehensive cancer information to those at risk and to patients, caregivers, and health care providers. This information ranges from prevention, through treatment, to end-of-life topics. For example, clinical sites across the country extensively use NIH print- and Web-based materials to support their educational programs. OCE also provides public affairs, publications, audiovisual exhibits, and Web development support to NCI Divisions, Offices, and Centers. The Cancer Information Service (CIS) effectively communicates information through a Partnership Program to help reach those with limited access to health information; an Information Service that provides cancer information by telephone, TTY, instant messaging, and e-mail; and a Research Program that helps advance health communication practices.

→ For more information, see http://www.cancer.gov/aboutnci/oce/
→ For more information, see http://cis.nci.nih.gov/
→ For more information, see http://cancer.gov/publications
→ For more information, see http://www.cancer.gov/cancertopics
→ For more information, see http://www.cancer.gov/espanol
→ This example also appears in Chapter 2: *Cancer*
→ (E) (**NCI**)

Exercise Guide for Older Americans: In January 2009, NIH offered an update of its popular exercise guide, newly titled *Exercise and Physical Activity: Your Everyday Guide from the National Institute on Aging*. The guide is the result of a 2-year process overseen by the Task Force on Exercise and Physical Activity, which included top scientists conducting research on exercise and physical activity in older adults, as well as representatives from key organizations involved in promoting exercise and physical activity to the public, including CDC, the American College of Sports Medicine, and the International Council on Active Aging. Based on an intensive review by these experts of the evidence on physical activity, the updated publication reviews in lively, easy-to-understand language the benefits of physical activity for older people, discusses the importance of regular effort and goal setting, provides specific activities and exercises appropriate for varying strength and skill levels, and includes worksheets to help the reader track his or her progress. The new guide is proving popular already with the public; between 2000 and 2008, NIH distributed 1.2 million copies while in 2009, NIH has distributed more than 300,000 copies of the guide. NIH is undertaking an outreach effort on exercise, with the guide as a foundation, to encourage older people to become more physically active.

→ For more information, see http://www.nia.nih.gov/Exercise
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (O) (**NIA**)

Health Information for Older Adults: NIH maintains a comprehensive program of health information aimed at older Americans. The NIA Information Center maintains a website and toll-free telephone lines to provide information in English and Spanish aimed at maintaining and improving health. Age Page fact sheets offer comprehensive, easy-to-read information on nearly 50 topics. The research update Spotlight on Aging Research (SOAR) provides current information on health and NIA activities to the public, policymakers, and researchers. The NIHSeniorHealth website enables the growing number of "wired seniors" to find credible aging-related health information in an online format that is compatible with their cognitive and visual needs, as determined by NIH-supported research; it includes 42 health topics developed by 12 NIH Institutes and one topic contributed by the Centers for Medicaid and Medicare. NIH also has developed a senior-friendly curriculum for people who train older adults to use computers. The Alzheimer's Disease Education and Referral (ADEAR) Center is the Federal government's primary source of information for patients, caregivers, health providers, policymakers, and the general public on Alzheimer's disease- and age-related cognitive change. The Center maintains a national database of clinical trials and develops easy-to-read materials in English and Spanish. In 2009, NIH collaborated with HBO Documentary Films, in association with the Alzheimer's Association, Fidelity Charitable Gift Fund, and Geoffrey Beene Gives Back Alzheimer's Initiative, on The Alzheimer's Project, which featured four documentary films, 33 supplemental films, a website, and a community-based information and outreach effort, with a companion book.

→ For more information, see http://www.nia.nih.gov/Alzheimers
→ For more information, see http://www.nia.nih.gov/HealthInformation/Publications
→ For more information, see http://www.NIHSeniorHealth.gov
→ (E) (**NIA**, NLM)

Know Stroke Efforts and New Stroke Slogan: In 2004, NIH entered a partnership with CDC to launch a grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders who work as "Stroke Champions" to educate their communities about the signs and symptoms of stroke and the need for immediate action. The program focuses on reaching African Americans, Hispanics, and seniors in communities that have the health care systems in place to treat stroke. To date, the program has been implemented in 12 cities, educating 184 Stroke Champions who have conducted more than 600 community events. The program was expanded this year to Charleston, South Carolina, and, as a follow-up to that program, materials will be developed for coastal communities with unique dialects. NIH also recently expanded its public education programs by collaborating with the Brain Attack Coalition (BAC) to develop a new action-oriented message that all member organizations could use with their current stroke awareness efforts. The BAC is a group of organizations committed to stroke prevention and treatment

chaired by NINDS. The new slogan—"Stroke strikes fast. You should too. Call 9-1-1."—was launched in May 2009 during Stroke Awareness Month.

→ For more information, see http://stroke.nih.gov/about/
→ This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Minority Health and Health Disparities*
→ (O) (**NINDS**)

Medicine in the Media Course: NIH presents a free annual training opportunity to help journalists evaluate and report on medical research. The program was created to address a growing need to improve the reporting of scientific and medical research findings by the media. Now in its eighth year, the course examines the challenges and opportunities inherent in the process of communicating the results of medical research to the public. The interactive program lays out the critical basics of differentiating strong from weak scientific information, well-designed vs. poorly-designed scientific studies, and "strength of opinion vs. strength of evidence." Stressing an evidence-based approach and re-examining intuitive beliefs about medicine, the course prepares participants for the crucial task of interpreting and evaluating research findings, including methods to select stories with meaningful messages for the public and place them in the appropriate context. Sessions are interactive, with hands-on opportunities to apply lessons learned, and incorporate journalists' unique perspectives on the public's need for useful medical knowledge. The program is highly competitive and attracts media and journalism professionals from around the country for a 3-day intensive workshop. Feedback from participants indicates that the program changed their fundamental understanding of what is worthy of reporting and helped them to provide appropriate context regarding the strengths, weaknesses, and relevance of a given study's findings. Participants frequently recommend the program to colleagues.

→ For more information, see http://medmediacourse.nih.gov/
→ For more information, see http://medmediacourse.nih.gov/02_agenda.html
→ (E) (**ODP/OMAR**)

National Child and Maternal Health Education Program (NCMHEP): To develop a national maternal and child health education program with input from stakeholders, NIH created a program to effectively review and translate maternal and child health research findings into new knowledge that can be disseminated to clinicians and their patients. Forums have been created in which major stakeholders in maternal and child health can work together to review scientific findings and decide how to best communicate their findings to targeted audiences. NIH has identified four areas on which the NCMHEP will focus: prematurity and low birth weight, pediatric obesity, infant mortality, and environmental influences on child health and development.

→ (O) (**NICHD**)

SIDS Outreach in Minority Communities: Since 1994, when NIH launched its campaign to reduce the risks of Sudden Infant Death Syndrome (SIDS), overall SIDS rates have declined significantly, yet the disparities continue to exist. Today, babies in the American Indian and Alaska Native communities are twice as likely to die from SIDS as white infants. To help eliminate this disparity, NIH, in collaboration with Native American Management Services, Inc., developed adaptable, culturally appropriate SIDS risk-reduction materials for use in five Indian Health Service Areas—Northern Tier-Aberdeen, Billings, Bemidji, Portland, and Alaska. Under the guidance of a community-based work group, educational materials have been developed based on recommendations from the five areas. The outreach project is called "Healthy Native Babies: Honoring the Past, Learning for the Future." Project materials include a training manual and a CD-ROM. The interactive CD-ROM that has been developed includes templates for a variety of SIDS risk-reduction educational materials. It contains photographs of American Indian and Alaska Native families and infants from the five regions, taken by local photographers. These photographs can be incorporated into educational materials such as posters, flyers, brochures, and postcards.

→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (O) (**NICHD**)

Science Education Partnership Award (SEPA) Program: SEPA increases the public's understanding of medical research by: 1) increasing the pipeline of future scientists and clinicians, especially from underserved and rural kindergarten to grade 12 (K-12) students, and 2) engaging and educating the general public on health-related advances made possible by NIH-funded research. By creating relationships among educators, museum curators, and medical researchers, SEPA encourages the development of hands-on, inquiry-based curricula that inform subjects about timely issues, including obesity, diabetes, stem cells, and emerging infectious diseases. Additionally, SEPA projects are designed to enhance public trust by focusing on topics such as the clinical trials process, patient safeguards, and medical research ethics. Through SEPA exhibits at science centers and museums, the program provides educational and community outreach activities to tens of thousands of people every year. In FY 2008, SEPA supported 68 projects, of which 50 targeted middle- and high-school students and 18 were based in science centers and museums.

→ For more information, see http://www.ncrr.nih.gov
→ For more information, see http://www.ncrrsepa.org
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NCRR**)

National Network of Libraries of Medicine (NN/LM): With more than 5,800 full and affiliate members representing academic health sciences libraries, hospital libraries, public libraries, and community-based organizations, the NN/LM plays a pivotal role in NIH's outreach programs to reduce health disparities and improve health information literacy. In FYs 2008-2009, NIH funded more than 400 community-based projects to enhance access to health information for health disparity and other medically underserved populations, building upon longstanding relationships with institutions providing health-related services and information to health disparity populations and developing many new relationships with schools, churches, public health departments, and others interested in improving health literacy and information access. Projects took place in rural and inner city communities and special populations in 35 states and the District of Columbia. The NN/LM also is a key player in the MedlinePlus "Go Local" service, which provides information about local community services to complement the nationally applicable health information in MedlinePlus. Go Local coverage reached 46 percent of the U.S. population in FYs 2008-2009. With an excellent track record of providing access to health information for clinicians and patients displaced by disasters, the NN/LM is the backbone of NIH's strategy to promote more effective use of libraries and librarians in local, State, and national disaster preparedness and response efforts. In FY 2008, a major initiative was the development of a national NN/LM Emergency Preparedness Plan to ensure backup health library services in the aftermath of a disaster and establish librarians as key community resources in disaster planning and response.

→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NLM**)

Minority Health Information Access: An NIH outreach goal is to reduce health disparities among African American, Hispanic, and Native American populations by using a variety of approaches to promote access to and use of health information among diverse communities. The Historically Black Colleges and Universities (HBCU) ACCESS Project, developed in partnership with the United Negro College Fund Special Programs, provides technical assistance, training, and funding for locally developed projects incorporating the use of NIH information resources in HBCU campuses and communities. The Environmental Health Information Partnership enhances the capacity of 20 academic institutions that provide health-related services and information to health disparity populations by supporting their efforts to reduce health disparities through the access and use of environmental health information. Projects to increase the knowledge of Native Hawaiian community members about health information were completed at the community of Miloli'I and Waimanolo

Health Center. At Cankdeska Cinkana Tribal College, Spirit Lake Nation, a health-related education program was developed along with tribal library improvements. Specialized websites, developed and expanded in partnership with community representatives, collect and organize information for specific populations such as Asian Americans, American Indians, and peoples of the Arctic. In the Lower Rio Grande Valley, the VIVA! Peer Tutors program at a magnet health high school is an award-winning effort to involve high school students in teaching their peers about online health information. The project has been extended to other schools and expanded to include promotion of health careers.

→ For more information, see http://sis.nlm.nih.gov/outreach.html
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (I) (**NLM**)

Rapidly Responding to Time-Sensitive Issues

Guidelines for the Medical Management of HIV: HHS issues Federal guidelines for the medical management of HIV infection and its associated co-infections, including antiretroviral treatment of HIV disease, prevention and treatment of opportunistic infections, and prevention of mother-to-child transmission of HIV. The guidelines are written, reviewed, and updated by working groups of the NIH OAR Advisory Council made up of HIV experts from across the country, including physicians, pharmacists, researchers, and community representatives. The guidelines represent the state of knowledge regarding the medical management of HIV disease in the United States. As the introduction and/or availability of new therapeutic agents, new clinical data, and emerging disease threats may change therapeutic options and preferences rapidly, the guidelines are updated frequently and are available as a "living document" on the AIDS*info* website. Updates that recently were added to the AIDS*info* website include the *FDA Alert: Use of Antivirals Tamiflu and Relenza in Children* and the *CDC Interim Guidance-HIV-Infected Adults and Adolescents: Considerations for Clinicians Regarding Novel Influenza A (H1N1) Virus*.

→ This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
→ (O) (**OAR**)

Recognizing Problems and Taking Action

It's a Noisy Planet. Protect Their Hearing: Approximately 26 million American adults are estimated to have high-frequency hearing loss caused by exposure to noise at work or during leisure activities. Since 1999, NIH has collaborated with the National Institute for Occupational Safety and Health on WISE EARS!®, a national education campaign to increase awareness about noise-induced hearing loss among the public and workers. In October 2008, NIH expanded these efforts by launching It's a Noisy Planet. Protect Their Hearing. This new campaign is designed to increase awareness among parents of children ages 8 to 12—or tweens—about the causes and prevention of noise-induced hearing loss. With this information, parents and other adults can encourage children to adopt healthy habits that will help them protect their hearing for life.

→ For more information, see http://www.noisyplanet.nidcd.nih.gov
→ (O) (**NIDCD**)

Providing Science-Based Oral Health Information: NIH provides science-based oral health information tailored to meet specific needs. Two examples are described here.

- *Practical Oral Care for People with Developmental Disabilities*: Finding dental care in the community is challenging for people with developmental disabilities. Many dentists do not feel trained sufficiently to provide services to people with special needs. To help increase access to dental care, NIH developed a series of publications to equip general dentists with information they need to deliver quality oral care to persons with developmental disabilities. The series includes continuing education (CE) programs for dentists and dental hygienists and a guide for caregivers describing

their important role in maintaining good oral health for their family member or client. The modules are so popular that NIH has extended the CE credit through 2011.

- *Spanish-Language Oral Health Website:* The Special Care Dentistry Association partners with NIH in this important health education outreach—Spanish-Language Oral Health Website. This new Spanish-language website tailored for U.S. Hispanics/Latinos increases Spanish speakers' access to science-based oral health information. The site recently was tested in two cities; participants were Spanish-dominant and bilingual Latinos with backgrounds from different countries of origin and with varying levels of education. The test was to ensure the new website is understandable, credible, and attractive to the intended audience. Other goals included understanding the approach Latinos take when seeking health information online, what they think of the quality of online health information, and whether there are significant differences between Spanish-dominant and bilingual individuals.

→ For more information, see http://www.nidcr.nih.gov/OralHealth/Topics/DevelopmentalDisabilities/
→ For more information, see http://www.nidcr.nih.gov/espanol
→ This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Minority Health and Health Disparities*
→ (O) (**NIDCR**, NICHD)

Reaching Out to Teens and Health Care Professionals: In the spring of 2009, NIDA unveiled NIDAMED, its first comprehensive physicians' outreach initiative. NIDAMED gives medical professionals a variety of information, including tools and resources, to help in screening patients for tobacco, alcohol, and illicit and nonmedical prescription drug use. The NIDAMED website contains links to numerous resources for health care professionals: an online screening tool titled NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NM ASSIST); two guides for clinicians (quick reference and a comprehensive resource guide); a number of key NIDA publications, such as the *Principles of Drug Abuse Treatment: A Research-Based Guide, The Science of Addiction, a Commonly Abused Drugs Chart,* and a postcard that encourages patients to "Tell Your Doctor About All the Drugs You Use." The NIDAMED initiative stresses the importance of the patient-doctor relationship in identifying and intervening early in patients' drug use behaviors before they evolve into life-threatening conditions. NIH is planning to hold its third annual Drug Facts Chat Day in November 2009. These events let students and teachers in classrooms across the United States ask questions of the Nation's top experts in the field of drug abuse and addiction. NIH staff will gather in a computer lab on the event day and will respond to submitted questions in real time. Chat Day events have proven to be a resounding success. The inaugural event elicited more than 35,000 questions.

→ For more information, see http://www.nida.nih.gov/nidamed
→ For more information, see http://www.nida.nih.gov/scienceofaddiction
→ For more information, see http://www.drugabuse.gov/chat
→ This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
→ (E) (**NIDA**)

Rethinking Drinking: To help people recognize and reduce their risk for alcohol problems, NIH recently launched an interactive website and supporting booklet, Rethinking Drinking. These new NIH resources offer evidence-based information about risky drinking patterns, the alcohol content of drinks, and the signs of an alcohol problem, along with information about medications and other resources to help people who choose to cut back or quit drinking. The website also provides tools, such as calculators that can be personalized by the user to estimate the alcohol content in common cocktails.

→ For more information, see http://rethinkingdrinking.niaaa.nih.gov
→ (E, O) (**NIAAA**)

Children and Clinical Studies: Medical research in children has saved lives and improved health and well-being, yet parents often are reluctant or uncertain about allowing their child to participate in a clinical study. The Children and Clinical Studies campaign helps parents and others to learn more about how clinical research is conducted in children, so that they can make well-informed decisions about whether to participate. Its website, which is available in English and Spanish, combines practical information with award-winning video footage of parents, health care providers, and children themselves discussing the rewards and challenges of participating in research. Educational materials for parents and health care providers can be requested through the site, as well.

→ For more information, see http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php
→ This example also appears in Chapter 3: *Technology Development*
→ (E) (**NHLBI**, NCRR, NICHD)

Partnering with Outside Organizations

Disaster Information Services: A Disaster Information Management Research Center was established in FY 2008 with the aim to facilitate access to disaster information, promote more effective use of libraries and disaster information specialists in disaster management efforts, and ensure uninterrupted access to critical health information resources when disasters occur. A disaster information website provides access to a broad range of emergency preparedness and response information. The Center also collaborates with the Navy National Medical Center, Suburban Hospital, Johns Hopkins Medicine, and NIH CC in the Bethesda Hospital Emergency Preparedness Partnership to provide backup communication systems and develop tools for patient tracking, information sharing and access, and responder training and to serve as a model for hospitals across the Nation. NIH also develops advanced information services and tools to assist emergency responders when disaster strikes. WISER (Wireless Information System for Emergency Responders) was developed for use during hazardous materials incidents and is available on the Internet or for downloading onto PDAs and PCs. Usage continues to grow, with more than 47,000 downloads onto PDAs in FY 2008. Radiation Event Medical Management (REMM) is a downloadable toolkit for use by health care providers during a mass casualty radiation event, with a version for mobile platforms released in FY 2008. Developed in collaboration with the HHS Office of Public Health Preparedness, REMM includes procedures for diagnosis and management of radiation contamination and exposure, guidance for use of radiation medical countermeasures, among other features to facilitate medical responses to radiation emergencies.

→ For more information, see http://disasterinfo.nlm.nih.gov
→ For more information, see http://wiser.nlm.nih.gov
→ For more information, see http://remm.nlm.gov
→ This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
→ (I) (**NLM**)

Partnerships for Environmental Public Health: NIH is developing a unified program referred to as "Partnerships for Environmental Public Health" (PEPH). PEPH will support activities to build new partnerships with community groups/stakeholders, develop and/or disseminate educational and outreach materials, enhance communication with partners (i.e., town meetings, forums on selected topics), evaluate (process and outcome evaluations) strategies to quantify public health impact, or engage community and researchers in Environmental Health Science research projects. The purpose of this program is to provide support for grantees already working in this area to enhance current grant activities within the scope of the peer-reviewed application and to encourage scientists with a traditional research focus to communicate/translate their research into materials or messages that are useful to other groups, such as the lay public, health care professionals, decisionmakers, or educators. Building partnerships and translating research to communities is an important component in promoting health and preventing exposures that may have adverse human health effects. By building environmental health and science literacy, community residents are better prepared and equipped to take personal and community action to reduce exposures. Partnerships between researchers and community groups foster trust and lead

to the identification of environmental health issues of concern to community residents, which may enhance the research results due to increased community participation.

→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (E) (**NIEHS**)

Outreach to the Scientific and Research Communities

AIDS Information Services: NIH manages the HHS-wide AIDS*info* service, which offers the latest federally approved information on HIV/AIDS clinical research, treatment and prevention, and medical practice guidelines that are developed by working groups under the auspices of the OAR Advisory Council. An AIDS*info* trans-agency steering group spans NIH, FDA, HRSA, and CDC. *Info*SIDA, a Spanish-language version, features a customized home page and a search engine that locates Spanish-language resources within AIDS*info*. A new initiative to incorporate tens of thousands of abstracts from AIDS-related conferences held over the last decade into NIH's Web-based electronic information services also is underway, and testing for the first public release of the new data was conducted in FY 2009. In addition to providing information systems, NIH supports community outreach programs for underserved communities and special populations to promote improved access to HIV/AIDS information for health professionals, patients, the affected community, caregivers, and the general public. Emphasis is placed on supporting community-based organizations, libraries, faith-based organizations, and health departments to design and implement local programs that include information access topics related to information retrieval, skills development, Internet access, resource development, and document access, e.g., through collaboration with local public libraries. In FYs 2008-2009, NIH made 25 community outreach awards.

→ For more information, see http://aidsinfo.nih.gov
→ For more information, see http://aidsinfo.nih.gov/infoSIDA/
→ For more information, see http://sis.nlm.nih.gov/outreach/hiv_outreach.html
→ This example also appears in Chapter 2: *Minority Health and Health Disparities*
→ (I) (**NLM**)

NIH Consensus Development Program: This program, administered by the Office of Medical Applications of Research (OMAR) within the Office of the Director, NIH, was established in 1977 as a mechanism to assess, translate, and disseminate the results of biomedical research. Since its inception, OMAR has conducted more than 120 Consensus Development Conferences, and 30 State-of-the-Science (formerly "Technology Assessment") Conferences. The program generates evidence-based statements addressing controversial issues in medicine and public health that are useful and relevant for health care providers, policymakers, patients, researchers, and the general public. The conferences are structured around key questions, including questions on the efficacy, risks, and clinical applications of a technology, along with current gaps in knowledge to help formulate directions for future research. For every conference, a systematic evidence review is performed through a partnership with the Agency for Healthcare Research and Quality to serve as the foundation upon which the conference will build. Experts in the field provide additional input and insights through several days of oral presentations. The conferences also contain sessions for public input and discussion. A multidisciplinary, nonadvocacy, independent panel free from scientific or financial conflicts considers all of this information, and then writes a statement answering the posed conference questions. Consensus and state-of-the-science statements are disseminated widely after the conference to either impact clinical practice—when evidence strongly supports the use (or avoidance) of a particular intervention—or to direct future research—when important gaps in knowledge have been identified. Upcoming conferences in 2010 include: Enhancing Use and Quality of Colorectal Cancer Screening; Lactose Intolerance and Health; Vaginal Birth After Cesarean: New Insights; Preventing Alzheimer's Disease and Cognitive Decline; and Inhaled Nitric Oxide Therapy for Preterm Infants.

→ For more information, see http://consensus.nih.gov/
→ This example also appears in Chapter 3: *Clinical and Translational Research*
→ (E) (**ODP/OMAR**)

Partners in Information Access for the Public Health Workforce (PH Partners): PH Partners, a 12-member public-private collaboration initiated by NIH, the Centers for Disease Control and Prevention, and the National Network of Libraries of Medicine assists the public health workforce to make effective use of electronic information sources. The Partners website, PHPartners.org, provides unified access to public health information resources produced by all members of the Partnership, as well as other reputable organizations. One of the most popular resources on the site is the Healthy People 2010 Information Access Project. In FY 2008, the website was expanded with more than 650 new links, and two new topic pages covering nutrition and workforce development were added.

→ For more information, see http://www.PHPartners.org
→ (I) (**NLM**)

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[64] The NIH National Resource Center is a partnership with support from NIA, the Eunice Kennedy Shriver NICHD, NIDCR, NIDDK, the NIH Office of Research on Women's Health, and the HHS Office on Women's Health.
[65] For more information, see http://www.health.gov/communication/literacy/issuebrief/.
[66] For more information, see http://nces.ed.gov/naal.
[67] For more information, see http://www.nih.gov/icd/od/ocpl/resources/healthliteracyresearch.htm.

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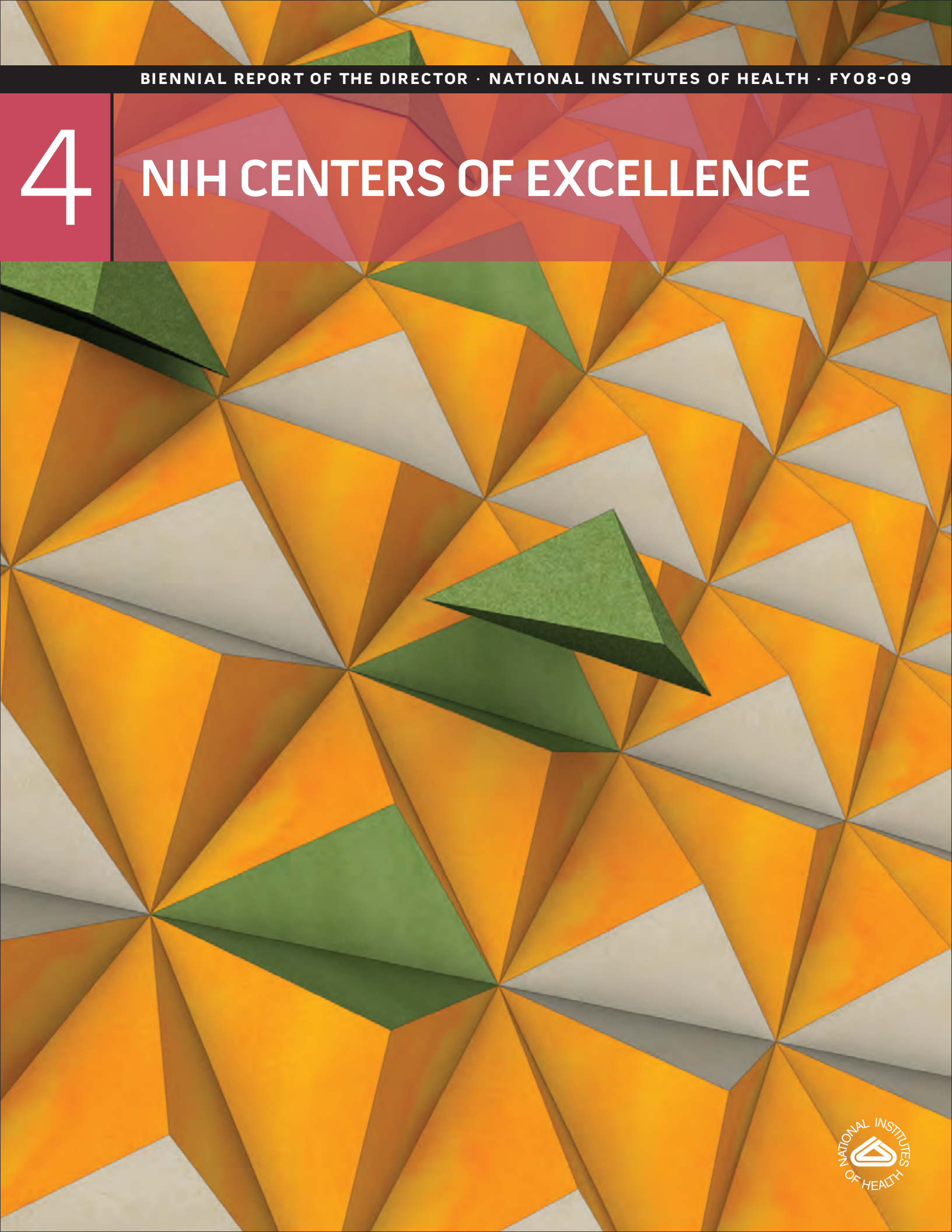
4 NIH CENTERS OF EXCELLENCE



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An electronic version of this report is available at: http://biennialreport.nih.gov and contains many live links to NIH programs, plans, and publications.

Volume IV Contents

Contents of Other Volumes

Introduction

NIH Centers of Excellence programs are diverse in focus, scope, and origin. In general, they facilitate and coordinate research efforts on a specific disease, a group of diseases, or an area of research. Some were created as NIH-wide initiatives, others by individual Institutes and Centers (ICs) and Offices within the NIH Office of the Director (NIH OD); some reflect mergers or redesignations of existing programs; and some were mandated by Congress. The NIH Centers of Excellence programs described in this report are a subset—those established by statutory mandate.

Some congressionally mandated Centers of Excellence programs focus on long-recognized, significant challenges to public health, such as Alzheimer's disease and other conditions that have a major impact on aging populations. Other such programs focus attention on areas of research that might otherwise be underfunded, such as rare diseases or health disparities. The mandated Centers of Excellence programs were established at different times and the number of research sites funded vary; thus, each of these programs differ in size, scope, accomplishments, and outcomes.

The Centers of Excellence programs help establish critical research infrastructure; foster collaboration; train researchers, physician scientists, and other professional staff; and provide shared resources, often through core facilities.

The specific research goals and activities of the mandated Centers of Excellence programs vary according to their authorization. In general, however, these programs help establish critical research infrastructure; foster collaboration; train researchers, physician scientists, and other professional staff; and provide shared resources, often through core facilities. Shared resources include systems for data gathering and analysis, instrumentation and computing, and the development of large patient registries. Research at the centers funded by these congressionally mandated programs often is multidisciplinary and designed to encourage scientists and clinicians from diverse fields to come together to focus on a common set of objectives.

All of the congressionally mandated NIH Centers of Excellence seek to integrate basic and translational research and to move those findings efficiently toward clinical applications, some of which are evaluated in patient populations brought together at the centers. Results from these studies may have spinoffs that increase knowledge about other areas of research. Through outreach and communication efforts, the centers inform researchers and the public of scientific advances and improvements in medical care. Administrative and program staff at individual ICs and Offices within the NIH OD oversee and manage each congressionally mandated NIH Centers of Excellence program. Specific centers funded under these mandated programs receive awards for a defined period of years, after which they must recompete for support.

The creation of Centers of Excellence at the discretion of NIH only takes place after an assessment of whether an adequate base of knowledge and number of expert investigators exists; what research opportunities are adequately supported through existing or planned funding mechanisms and initiatives; and the appropriateness of alternative funding mechanisms. Recognizing that it should only create Centers of Excellence under certain circumstances, Congress provided the NIH Director with a new authority, through the NIH Reform Act of 2006, to review and approve the establishment of all Centers of Excellence recommended by the agency's ICs and Offices within the NIH OD.

This chapter provides overviews, progress reports for the FYs 2008 and 2009 biennial period (covering programmatic and research activities and outcomes), recommendations, evaluation plans, and future directions for the six congressionally mandated NIH Centers of Excellence programs, which are described in the order of their establishment:

- Alzheimer's Disease Centers (1984)
- Claude D. Pepper Older Americans Independence Centers of Excellence (1989)
- Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (2001)
- National Center on Minority Health and Health Disparities Centers of Excellence (2001)

- Rare Diseases Clinical Research Network (2003)
- New Autism Centers of Excellence (2006), which merged the previously existing Collaborative Programs of Excellence in Autism and Studies to Advance Autism Research and Treatment

Tables listing the centers funded under each mandated Centers of Excellence program appear at the end of the narrative on each program.

Alzheimer's Disease Centers

Overview

Why the ADCs Were Established

In 1984, Congress directed NIH to foster further research related to Alzheimer's disease (AD). The Public Health Service Act authorizes the NIH Alzheimer's Disease Centers (ADCs) program under section 445 (42 U.S.C. 285e-2). NIH funded the first ADCs in the mid-1980s in response to the congressional directive, information on AD emerging from the work of NIH grantees and other researchers, and the prospect of a medical and social crisis triggered by an explosion of AD cases as the population ages. The principal objectives of the ADC program are to promote research, research, training, outreach, and technology transfer. Much of the research takes place through multicenter cooperative studies to better understand the causes and effects of AD and to develop and test new interventions for the diagnosis, treatment, and prevention of AD and other age-related neurodegenerative diseases (diseases in which the cells of the brain and spinal cord are lost) and normal aging.

How the ADCs Function Within the NIH Framework

NIH currently funds 30 ADCs (see Table 4-1). Funding for the ADCs comes from NIA through the P30 (center core grant) and P50 (specialized center grant) mechanisms for 5 years and then must compete through a peer review process for additional funding. New applicants for ADCs compete with existing grantees. If existing centers are unsuccessful in competition, new centers are funded to take their places.

NIH currently funds 30 Alzheimer's Disease Centers through a congressionally mandated program initiated in 1984.

Description of Disease or Condition

AD is the most common form of dementia among older people. It is an age-related, irreversible brain disorder that develops over many years. In the very early stage, people experience memory loss, which can be mistaken for memory changes that occur in normal aging. As the disease progresses, these symptoms gradually lead to dementia, a condition characterized by marked memory loss and behavior and personality changes. The disease also leads to a decline in other cognitive abilities (such as decision-making and language skills) and, eventually, an inability to recognize family and friends and a severe loss of mental function. These losses are related to the breakdown of the connections between neurons (nerve cells) in the brain and to the eventual death of many of these cells. In most people, symptoms first appear after age 60. AD and other dementing disorders are caused by disease processes that affect the brain, although age-related brain and body changes also can affect the development of AD and other dementias.

AD is named after Dr. Alois Alzheimer, a German doctor who, more than 100 years ago, studied the brain tissue of a woman who had died of an unexplained mental illness. Dr. Alzheimer found unusual features of her brain tissue—many deposits of sticky proteins in the spaces between neurons, now known as beta-amyloid plaques, and tangled bundles of fibrils (thin fibers) within neurons, now known as neurofibrillary tangles. However, it was not until the 1960s and 1970s that scientists began to recognize AD as a disease associated with aging.[1] Today, plaques and tangles in the brain are considered signs of AD, as are other brain changes, including the death of neurons in areas of the brain that are vital to memory and other mental abilities and the disruption of connections, called synapses, that allow neurons to communicate with each other. The disease also is characterized by low levels of some of the chemicals in the brain that carry messages between neurons. AD impairs thinking and memory by disrupting these messages.

Scientists are finding evidence that some of the risk factors for heart disease and stroke—such as high blood pressure, high cholesterol, and low levels of the vitamin folate—might increase the risk for AD. Evidence also is increasing that physical, mental, and social activities may protect people from AD.

AD probably has no single cause. The most important known risk factors are age and family history, although education, diet, and environment also might play a role. Scientists also are finding evidence that some of the risk factors for heart disease and stroke—such as high blood pressure, high cholesterol, and low levels of the vitamin folate—might increase the risk for AD. Evidence also is increasing that physical, mental, and social activities may protect people from AD. Although scientists have learned a great deal about AD, they still do not know what causes the disease and have not identified a cure.

Burden of Illness

Recent estimates from a nationally representative sample in the Aging, Demographics, and Memory Study (part of the ongoing NIH-supported Health and Retirement Study) suggest that one in seven Americans age 72 or older has dementia and about 2.4 million have AD.[2] Other investigators, using projections from community-based studies, estimate that 5.1 million Americans ages 65 or older will have AD in 2010.[3] Despite the differing methodologies and results of their studies, experts agree that the number of people with AD will increase significantly if current U.S. population trends continue and no prevention methods emerge. Our aging society makes AD an especially critical issue because the number of people with the disease doubles for every 5-year age interval beyond age 65. The U.S. Census Bureau estimates that the size of the population ages 65 and older will double to about 72 million people in the next 25 years. Moreover, the fastest growing segment of the U.S. population is comprised of people 85 years of age or older.

Scope of NIH Activities: Research and Programmatic

The ADC program provides infrastructure and core resources to enhance ongoing research by bringing together basic biomedical, behavioral, and clinical scientists to study the causes, progression, prevention, diagnosis, and treatment of AD and to improve health care delivery. ADCs also foster the development of new research approaches and provide suitable environments for research fellows and junior faculty to acquire the necessary skills and experience for interdisciplinary AD research.

NIH requires all 30 ADCs to have the following cores: administrative, clinical, data management and statistics, education and information transfer, and neuropathology. Some centers include other optional cores, such as neuroimaging or genetics cores, and some have satellite diagnostic and treatment clinics to help recruit minority or rural research participants.

The ADC program comprises two types of centers. Alzheimer's Disease Research Centers conduct research projects in addition to providing core resources. The Alzheimer's Disease Core Centers consist of cores only and provide investigators with access to well-characterized patients, patient and family information, and tissue and other biological specimens for use in separately funded research projects.

By pooling resources and working cooperatively with other ADCs, these centers have produced research findings and developed resources that individual investigators working alone could not have achieved.

By pooling resources and working cooperatively with other ADCs, these centers have produced research findings and developed resources that individual investigators working alone could not have achieved. ADCs have provided biological samples from patients with AD for hundreds of non-ADC funded projects. Several major long-term studies on the development of dementia in specific populations rely on ADC core facilities and integrate their findings with those of the centers.

Examples of resources shared among ADCs are the brain and specimen banks at each center, which consist of well-characterized specimens collected under standardized protocols. Another resource shared by the ADCs is the National Cell Repository for Alzheimer's Disease (NCRAD) at Indiana University, which collects and stores blood, DNA, and cell lines from families with several affected members and from unaffected control participants. NCRAD also stores well-documented phenotypic data, which includes the observable traits or characteristics of a person, such as age and gender, as well as the presence or absence of a disease. The repository is part of the NIH Alzheimer's Disease Genetics Initiative, which was established to identify genetic risk factors for late-onset AD, and the recently funded Alzheimer's Disease Genetics Consortium, which conducts large-scale whole-genome studies on AD.

The ADCs have helped create additional collaborative research resources or projects, such as the Consortium to Establish a Registry for Alzheimer's Disease, the National Alzheimer's Coordinating Center, the Alzheimer's Disease Cooperative Study, and the Alzheimer's Disease Neuroimaging Initiative. Descriptions of these and other efforts are provided below.

Much important progress in AD research in the United States during the past 25 years stems from research conducted at the ADCs, as well as from resources and infrastructure provided by the centers. Through ADC research, scientists have identified mutant genes on three chromosomes whose presence could result in the rare early-onset, inherited AD; discovered a version of a gene on chromosome 19 that is a risk factor for the more common late-onset AD; and determined that mutant genes on chromosome 17 are associated with frontotemporal dementia, a group of rare dementia disorders that affect the parts of the brain that are associated with language and behavior. Other studies have revealed the importance of the abnormal processing of proteins encoded by these genes.

Through ADC research, scientists have identified mutant genes on three chromosomes whose presence could result in the rare early-onset, inherited AD and discovered a version of a gene on chromosome 19 that is a risk factor for the more common late-onset AD.

ADC scientists have conducted much of the research on protein processing related to plaque and tangle formation, including the discovery of a protein implicated in the development of Lewy body dementia (which can cause confusion, rigid muscles, slower movement, and tremors). ADC researchers also identified the common properties of the abnormal proteins associated with several neurodegenerative diseases, which are characterized by damage or loss of neurons in the brain and spinal cord. Additional support through ARRA funding to the Johns Hopkins ADC will enhance research efforts in studies of brain pathology.

In recent years, ADC researchers have evaluated cognitive changes associated with normal aging and the transitions to mild cognitive impairment (early difficulties with thinking and remembering) and dementia. They also have identified factors that contribute to changes in cognitive abilities.

Currently, many ADCs are carrying out important studies relating changes in brain structure to different clinical stages of AD. For these studies, researchers are examining patients enrolled in the clinical cores, brain imaging supported by imaging cores, and autopsy evaluations in neuropathology cores. ADC researchers also are examining relationships and commonalities between AD and cerebrovascular disease or other neurodegenerative diseases as well as contributions of co-existing non-neurological conditions that occur in people with AD.

The ADCs are exploring commonalities between AD and other dementias that involve Lewy bodies and between AD and Parkinson's disease dementia. In this regard, collaborations are underway with the NINDS-supported Udall Parkinson's Disease Centers to examine the overlapping scientific and clinical issues.

Many (18) ADCs also participate in the NIH Late Onset Alzheimer's Disease (LOAD) Genetics Initiative, which was launched to help advance AD-related genetics research. LOAD aims to collect samples from more than 1,000 families having at least two members with late-onset AD as well as 1,000 control participants. The Columbia University AD Research Center serves as the coordination center for LOAD. To complete enrollment, characterization, and follow-up of

patients and control participants in the LOAD Genetics Initiative, NIH awarded a resource grant to a consortium of six ADCs. As of 2009, more than 5,000 new blood samples from approximately 800 late-onset AD families have been sent to the National Cell Repository for Alzheimer's Disease, another important resource for the ADCs. In a search for risk factor genes, ADC researchers are analyzing data derived from whole-genome scans of LOAD samples.

The ADCs are contributing phenotypic information and DNA specimens from participants enrolled in ADC studies to a major new genomic project carried out by the NIH-funded Alzheimer's Disease Genetics Consortium, which will perform whole-genome scans using specimens from up to 10,000 human subjects enrolled in the ADCs as well as from other major population studies.

The ADCs also are contributing phenotypic information and DNA specimens from participants enrolled in ADC studies to a major new genomic project carried out by the NIH-funded Alzheimer's Disease Genetics Consortium (ADGC). The ADGC will perform whole-genome scans using specimens from up to 10,000 human subjects enrolled in the ADCs as well as from other major population studies. In FY 2009, ARRA funds were awarded to the ADGC to add 3,800 AD patients and an equal number of people free of disease, thus making this one of the largest collections of samples available for genome-wide association studies in an effort to identify the susceptibility and protective genes influencing the onset and progression of late-onset disease.

Another major objective for the ADCs is to recruit minority and ethnically diverse research participants for AD research. To achieve this goal, NIH created the Satellite Diagnostic and Treatment Clinics and linked them to the ADCs. The number of satellites has fluctuated; 23 currently are active and are recruiting African American, Hispanic, Native American, and Asian research participants. National Alzheimer's Coordinating Center data now show that approximately 20 percent of those enrolled in the ADCs are minorities. Also, the ADCs conduct research related to minority concerns in cooperation with the NIH-supported Research Centers on Minority Aging Research. In addition, ARRA funds were awarded to two ADCs to help understand the factors that affect recruitment of minority populations in their studies. These two supplements will be used to study recruitment of African American participants at a satellite clinic at the University of Kentucky's ADC and at the Boston University ADC.

National Alzheimer's Coordinating Center data now show that approximately 20 percent of those enrolled in the ADCs are minorities.

All ADCs have Education and Information Transfer Cores (EITCs) that provide research training for new investigators, as well as outreach to the public, including caregivers. EITC efforts also have been redefined recently to facilitate participant recruitment for projects such as the NIA Genetics Initiative, Alzheimer's Disease Cooperative Study, Alzheimer's Disease Neuroimaging Initiative, and other clinical trials and initiatives. Collaborations include ongoing interactions with groups such as the Alzheimer's Association and NIH's Alzheimer's Disease Education and Referral Center. The ADCs pay special attention to cultural sensitivity and, where appropriate, structure their information to effectively reach minority populations, including non-English-speaking people.

The three New York City ADCs—at Columbia University, Mount Sinai School of Medicine, and New York University—and the New York City chapter of the Alzheimer's Association jointly formed the New York Consortium for Alzheimer's Research and Education in 2000. The consortium provides continuing medical education programs for community physicians on AD diagnosis, management, and research opportunities.

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the ADCs was $51.0 million in FY 2008 and $51.9 million in FY 2009, including $0.7 million from ARRA funds.

FY 2008 and FY 2009 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments for the ADCs include the following examples.

- **National Alzheimer's Coordinating Center (NACC):** In 1999, NIH established NACC to facilitate collaborative research and standardize procedures among the ADCs. NACC developed and maintains a large database of standardized clinical and neuropathological research data collected from each ADC. This database provides a valuable resource to qualified research scientists for both exploratory and explanatory AD research. The data provided by NACC support large studies that use patient samples from diverse populations and multiple ADCs. NACC collects standardized data (the Uniform Data Set or UDS) collected over time from research participants who are examined annually.

  Currently, the ADCs are following about 15,000 research participants, and NACC is storing these data. NACC has adopted new procedures for widening access to the database by non-center scientists. NACC has funded 18 collaborative multicenter studies using its own resources, and an additional 8 NIH-funded collaborative research project R01 grants are linked to NACC.

- **Alzheimer's Disease Cooperative Study (ADCS):** All of the ADCs are performance sites for the ADCS, which is the cornerstone of NIH's major AD clinical trials effort. ADCS is a large clinical trials consortium that expanded from the ADCs and now includes sites throughout the United States and Canada. The clinical research outcomes of ADCs are inextricable from the outcomes of ADCS.

  NIH developed the ADCS to advance research on drugs that might be useful for treating patients with AD, particularly drugs that industry might not develop. The study tests agents that lack patent protection; drugs that are under patent protection but marketed by manufacturers for other diseases; and novel compounds developed by individuals, academic institutions, and small biotechnology companies. The ADCS also develops new evaluation instruments for clinical trials, as well as novel approaches to clinical trial design.

  Since its inception, the ADCS has initiated 30 research studies, 23 drug trials, and 7 instrument-development protocols. Studies currently underway at ADC performance sites include:

  - A trial examining whether treatment with docosahexaenoic acid, an omega-3 fatty acid, will slow decline in AD.
  - A trial evaluating the efficacy and safety of intravenous immunoglobulin, which contains naturally occurring antibodies against beta-amyloid, in patients with mild-to-moderate AD.
  - A multicenter trial evaluating home-based assessment methods for AD prevention research in people ages 75 and older.

- **Alzheimer's Disease Neuroimaging Initiative (ADNI):** Most ADCs participate in ADNI, which is an innovative public-private partnership that is examining the potential of serial magnetic resonance imaging (MRI), positron emission tomography (PET), or biomarkers to measure earlier, and with greater sensitivity, the development and progression of mild cognitive impairment and AD. As is true of the ADCS, the activities and outcomes of ADNI are inextricable from those of the ADCs. ADNI completed enrollment in August 2007 and now is monitoring the 823 participants using MRI and PET imaging and laboratory and cognitive tests. This will generate a comprehensive database that will serve as an important public resource to spur further research. Already, many of the tools and methods developed by the study are fueling similar efforts in Japan, the European Union, and Australia.

  In 2007, ADNI obtained additional funds to conduct a genome-wide association study (GWAS) and analyze the genetic variations among ADNI participants. This effort will provide the most extensive and robust dataset of its kind in AD research and will be a critical resource for ADC investigators among others. Supplemental funding from NIH allows the collection of cerebrospinal fluid from participants, while funding from a third NIH supplement is used to

explore the use of PET imaging and Pittsburgh compound B (PiB, an amyloid imaging agent) as tools for developing biochemical and imaging markers.

Results from an ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid might signal the onset of mild AD and established methods and standards for testing these biomarkers (see "Research Accomplishments" for more details). More than 1,000 researchers, as well as other interested individuals, already have accessed a public database containing thousands of brain images, related clinical data, and blood and cerebrospinal fluid analyses.

In FY 2009, ARRA funds were awarded to ADNI to expand the scope of ongoing research by allowing for the enrollment of participants at an earlier stage of mild cognitive impairment (MCI), when symptoms are milder. Furthermore, the funding for this new grant will allow ADNI investigators to extend the length of the original study to better assess changes in individuals over time. The overall impact of the added funding will be increased knowledge of the sequence and timing of events leading to MCI and Alzheimer's disease and development of better clinical and imaging/fluid biomarker methods for early detection and for monitoring the progression of these conditions. This will facilitate clinical trials of treatments to slow disease progression and ultimately will contribute to the prevention of Alzheimer's disease.

Research Activities and Outcomes

Since the establishment of the ADC program in 1984, investigators have published thousands of research papers on all aspects of AD and related disorders. Topics have ranged from the disease's biology to its family and societal impact, as well as many studies of diagnosis and treatment.

Research accomplishments include the following important recent studies carried out by ADC scientists, which highlight research on biomarkers and AD recently carried out by several centers. These studies are only a few examples from a wide spectrum of research studies conducted by the ADCs.

- **Beta Amyloid Deposition Imaging.**[4] The progressive accumulation of a protein called beta amyloid in the brain is a hallmark of AD. Previously, a researcher's ability to measure the amount of beta amyloid in a person's brain could only be accomplished at autopsy. Now, with the development of the new tracer element PiB (Pittsburgh Compound B), researchers can visualize the amount of beta amyloid in the brains of living people. Investigators at the University of Pittsburgh ADC studied PiB binding in the brain using PET imaging to visualize beta amyloid in the brains of living people over age 65. The participants did not have symptoms of AD or other less severe forms of dementia, such as mild cognitive impairment. Of the brains imaged, 21 percent showed evidence of early amyloid deposition in at least one brain area. Demographic characteristics such as gender did not differ significantly between those with and without beta amyloid in their brains. Importantly, the researchers were able to demonstrate that beta amyloid can be identified in the brains of cognitively normal older persons during life and that some older persons can remain cognitively normal despite a significant amount of beta amyloid within their brains. Further studies over a longer period of time now are necessary to ascertain the potential of PiB imaging to identify preclinical AD or, alternatively, to show that beta amyloid deposition alone is not sufficient to predict AD in the future.

Previously, a researcher's ability to measure the amount of beta amyloid in a person's brain could only be accomplished at autopsy. Now, with the development of the new tracer element PiB (Pittsburgh Compound B), researchers can visualize the amount of beta amyloid in the brains of living people.

- **Biomarkers of Presymptomatic AD.**[5] For AD treatments to have the greatest impact, health care providers will need to treat individuals before symptoms appear. Investigators are exploring fluid and neuroimaging measures as possible biomarkers of AD pathology that could aid in identifying individuals during the earliest stages of their disease to direct and monitor therapy. For example, researchers at the Washington University ADC investigated the relationship between brain volume (as measured by MRI) and an array of proteins that are implicated in the eventual development of AD in cognitively normal participants and individuals who have been diagnosed with early AD. They recently

found that lower levels of the toxic protein fragment amyloid beta-42 in cerebrospinal fluid (CSF)—a colorless fluid that circulates through and around the central nervous system, including the brain—in cognitively normal people appear to be associated with lower brain volume, suggesting some damage to the brain. The study indicates that increases in the protein tau take place later in the course of the disease and are more closely associated with clinical onset and progression of AD. Taken together, these results provide additional evidence that amyloid-associated brain damage may occur well before clinical symptoms appear.

- **Cerebrospinal Fluid Biomarkers.**[6] In the first ADNI CSF biomarker study, NIH-supported researchers, including ADC researchers, established a method and standard for testing levels of two candidate biomarkers for AD—tau and beta amyloid proteins, which are potential biomarkers for AD in the brain and the CSF. The researchers now have correlated levels of these proteins in CSF with changes in cognition over time and determined that changes in these two protein levels in CSF may signal the onset of mild AD. This is a significant step forward in developing a test to help diagnose the early stages of AD sooner and more accurately to begin treatment that could delay the development of more severe AD symptoms. In fact, this effort may open the door to the discovery of an entire panel of CSF biomarkers that will not only identify people at risk of developing AD, but also assess how the disease responds to therapies. Importantly, these data are available online to qualified researchers worldwide.

Researchers have correlated levels of two proteins in cerebrospinal fluid with changes in cognition over time and determined that changes in these two protein levels may signal the onset of mild AD.

- **Measuring the Effects of AD Treatment.**[7] Recently, ADC investigators used a new method of stable isotope labeling in which they "tagged" molecules in a compound with a radioactive tracer to assess the effects of an experimental drug on the production and clearance rates of proteins that are implicated in the development of AD and other central nervous system (CNS) disorders. The results from this approach might help investigators make decisions about drug effectiveness and dosing in designing larger and longer clinical trials for diseases such as AD and may accelerate effective drug validation. Notably, this is the first time that investigators have been able to measure directly over time the reduction of beta amyloid in CSF by a drug that typically inhibits its production. This approach provides a means for testing the relative effects of dose and drug in current and novel therapeutic agents.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the ADCs

Since their launch in 1984, the NIH ADCs have continued to grow, and many multicenter initiatives have begun. In 2008, the National Advisory Council on Aging, an external advisory committee, reviewed the program's progress in achieving recommendations made in 2002. The council suggested that NIH examine the need to revise clinical diagnostic criteria for AD for identifying people with AD at an earlier stage in its development so that clinicians can prescribe strategies for delaying the onset of AD. That initiative is currently underway.

Evaluation Plans

The National Advisory Council on Aging evaluates and makes recommendations for the ADC program every 4 years. The next evaluation will be in 2012.

Future Directions

NIH plans for the ADCs to continue to place less emphasis on late-stage AD and will concentrate instead on the transition from normal aging to mild cognitive impairment and to full-blown AD, as well as on studies of the overlap between AD and other neurodegenerative diseases. In addition, the ADCs will continue to search for biomarkers that predict cognitive decline and diagnose cognitive impairment and dementia. NIH will continue to support existing ADCs, which must recompete for funding after each grant cycle (typically every 5 years) and award new grants to institutions that the NIH peer-review process deems to be qualified.

Table 4-1. Alzheimer's Disease Centers of Excellence (ADCs)

Institution and Location	Year Established
University of California, San Diego, CA	1984
Massachusetts General Hospital, Boston, MA	1984
Mount Sinai School of Medicine, New York, NY	1984
University of Southern California, Los Angeles, CA	1984
Johns Hopkins University, Baltimore, MD	1984
Duke University, Durham, NC	1985
University of Kentucky, Lexington, KY	1985
University of Pittsburgh, Pittsburgh, PA	1985
University of Washington, Seattle, WA	1985
Washington University in St. Louis, MO	1985
University of Texas Southwestern Medical Center, Dallas, TX	1988
University of Michigan, Ann Arbor, MI	1989
Columbia University Health Sciences, New York, NY	1989
Oregon Health & Science University, Portland, OR	1990
New York University School of Medicine, New York, NY	1990
Mayo Clinic College of Medicine, Rochester, NY	1990
University of Pennsylvania, Philadelphia, PA	1991
University of California Davis School of Medicine, Sacramento, CA	1991
Indiana University-Purdue University, Indianapolis, IN	1991
Rush University Medical Center, Chicago, IL	1991
University of California, Los Angeles, CA	1991
Boston University Medical Campus, Boston, MA	1996
Northwestern University, Chicago, IL	1996
University of Alabama, Birmingham, AL	1999
University of California, Irvine, CA	2000
Arizona Alzheimer’s Center, Phoenix, AZ	2001

Alzheimer's Disease Centers

Institution and Location	Year Established
University of California, San Francisco, CA	2004
Emory University, Atlanta, GA	2005
Florida Alzheimer's Center, Tampa, FL	2005
University of Wisconsin, Madison, WI	2009

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Claude D. Pepper Older Americans Independence Centers

Overview

Why the OAICs Were Established

In 1955, the U.S. Surgeon General established five Geriatric Research and Training Centers to advance research on the health care problems of the elderly and to train future academic leaders in geriatrics. In 1989, Congress enacted legislation that redesignated the Geriatric Research and Training Centers as the Claude D. Pepper Older Americans Independence Centers (OAICs), in honor of former Florida Senator and Representative Claude Denson Pepper for his efforts to promote the health and well-being of older Americans. Section 445A of the Public Health Service Act (42 U.S.C. 285e-3) authorizes the OAICs, which NIH funds for 5-year periods, to increase scientific knowledge leading to better ways to maintain or restore independence in older adults (see Table 4-2).

How OAICs Function within the NIH Framework

NIH funding for the OAICs comes from NIA through a center grant mechanism (P30). The ultimate goal of the OAIC program is to translate research on aging to applications and interventions that increase or maintain independence for older persons. NIH currently funds 30 ADCs (see Table 4-1).

As Centers of Excellence in geriatrics research and training, the OAICs provide intellectual leadership in geriatrics research, encouraging and facilitating multidisciplinary and interdisciplinary collaborations in basic, translational, and clinical research relevant to the health and independence of older persons. In addition, each OAIC includes a Research Career Development Core to provide research training and career development opportunities in geriatrics and related fields.

Description of Disease or Condition

Aging research focuses on a range of conditions, including geriatric syndromes—such as involuntary weight loss, dizziness, and incontinence—and diseases and disorders that are more common among older adults—such as cancer, cardiovascular disorders, stroke, and loss of sensory functions, such as hearing and sight.

By 2030, the number of individuals age 65 or older is likely to double to 70.3 million, and this group will comprise 20 percent of the entire U.S. population, in contrast to 13 percent today.

Burden of Illness

Currently, 35 million Americans are older than 65 years. Of these, more than 4 million are older than 85, and approximately 65,000 have reached their 100th birthday. By 2030, the number of individuals age 65 or older is likely to double to 70.3 million, and this group will comprise 20 percent of the entire U.S. population, in contrast to 13 percent today. The number of the "oldest old"—people age 85 or older—is expected to grow to at least 20.9 million by 2050.[8]

Today, half of all Americans older than age 65 show evidence of osteoarthritis in at least one joint.[9] More than half of Americans older than age 50 have osteoporosis or low bone mass.[10] Cardiovascular disease, cancer, and diabetes remain common among older Americans.

The ratio of older people to other age groups is important to society because older people, particularly the oldest old, sometimes depend on family members, the government, or both for financial, physical, and emotional support. In addition, a large part of older people's well-being depends on programs such as Social Security and Medicare, which are financed through the contributions of working-age individuals. When the entire population of baby boomers enters older age,

around 2030, the challenge to meet their needs through social, governmental, and other health care services will expand markedly.[11]

As life expectancy increases, the health care system will need new ways to minimize disease and disability during the additional years of life.

In 2006, U.S. health care expenditures totaled approximately $2.1 trillion, more than in any other industrialized country.[12] Researchers predict that increased longevity is likely to require more financing from Federal health care systems, including Medicare and Medicaid.[13] As life expectancy increases, the health care system will need new ways to minimize disease and disability during the additional years of life.

Scope of NIH Activities: Research and Programmatic

OAICs are designed to develop or strengthen each awardee institution's programs in a key area of aging research, contribute to greater independence for older persons, and offer opportunities for training and career development in aging research for young scientists. The program's ultimate goal is to enhance translation of basic and developmental research on aging to applications and interventions that increase or maintain independence for older persons.

NIH expects each OAIC, in its selected area of focus, to:

- Provide intellectual leadership and innovation in geriatrics
- Stimulate translation of basic and clinical research in aging
- Facilitate and develop novel multidisciplinary and interdisciplinary research strategies to address current issues in geriatrics care
- Stimulate incorporation of emerging technologies, methods, and scientific advances into research designs
- Serve as a source of advice and collaboration to other institutions regarding technology, methodology, analysis, or other expertise relevant to research in aging
- Provide research training and career development for future leaders in geriatrics research

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the OAICs was $14.0 million in FY 2008 and $14.3 million in FY 2009, including $0.4 million from ARRA funds.

FY 2008 and FY 2009 Progress Report

Programmatic and Research Activities and Outcome

- The **University of Florida OAIC** focuses its aging research on sarcopenia (age-related muscle loss), including biological mechanisms and contributing factors, as well as the prevention and rehabilitation of disability resulting from sarcopenia. University of Florida researchers examine these issues from interdisciplinary perspectives across the entire spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral and social sciences, and epidemiology. One ongoing project is evaluating interventions that change fat concentrations in aged rats to assess their effects on physical function, inflammation, damage to cells from free radicals (destructive molecules), cell death, and sarcopenia. This study could lead to testing of other interventions to lower fat concentrations in animals and to study the effect of reduced fat on age-related outcomes. Another project could help in the development of a novel, safe, and practical intervention to reduce muscle loss among older people by improving muscle function without high-intensity exercise.
- The **Boston Medical Center at Boston University** recently received a grant to establish an OAIC in collaboration with Tufts University, the Joslin Clinic, and the New England Research Institute. The central research theme of the new OAIC is to develop therapies that improve muscle function. Currently, few if any drugs or therapies are available

to improve muscle strength, mobility, and physical function for frail older people. The OAIC at Boston University will foster collaborations among the university's multidisciplinary team of investigators to improve physical mobility by covering the entire spectrum of drug discovery, from target identification to clinical trials and function-promoting therapies. For example, one project will recruit frail, elderly, vitamin D-deficient women to determine whether vitamin D supplements improve outcomes.

- The **University of Pittsburgh OAIC** provides support and resources for investigators to study balance disorders in the elderly. This OAIC provides an integrated, multidisciplinary approach by pulling resources from five schools at the University of Pittsburgh. The center's long-range goals are to incorporate into clinical care and wellness programs in diverse settings effective interventions to maintain or improve balance and reduce the negative consequences of balance disorders. In addition, the center aims to further define an approach to identify factors that contribute to balance disorders for use in prevention and treatment.

Growing evidence indicates that aging and functional decline might involve changes in the body's physical and chemical processing of lipids, or fatty substances, but scientists do not yet understand these changes. One current project is enhancing the ability to analyze lipid processing in body fluids and tissue samples from animals and people.

- The theme of the **Duke University OAIC** is to understand and modify different causes of decline in physical functioning. The Duke OAIC develops and evaluates interventions designed to help older Americans prepare for, cope with, and recover from disability arising from late-life disease and aging. Growing evidence indicates that aging and functional decline might involve changes in the body's physical and chemical processing of lipids, or fatty substances, but scientists do not yet understand these changes. One current project is enhancing the ability to analyze lipid processing in body fluids and tissue samples from animals and people.
- The **Johns Hopkins University OAIC** supports research to determine the causes of and potential interventions to reduce frailty in older adults. To support frailty intervention studies, the university created a clinical translation unit and a registry of older adults who might be willing to participate in research. The Johns Hopkins OAIC has established state-of-the-art infrastructure to generate genetic data and analyses related to frailty and has assembled a multidisciplinary team of experienced investigators. The center also has identified new markers of frailty, identified critical biological causes of frailty, and developed a strain of frail mice that investigators can use for research.
- The **University of California, Los Angeles OAIC** supports the development and testing of interventions to prevent disability. The center emphasizes research that builds bridges between basic biomedical science and clinical science. Current projects are addressing the underlying causes of bone loss in osteoporosis and the effects of stroke on nerve-repair genes in the aged brain.
- The **University of Maryland, Baltimore OAIC** is studying rehabilitation approaches involving exercise and motor learning. The goal is to improve the recovery of older adults who have suffered a stroke, hip fracture, or other chronic debilitating disease. The center plans to translate these findings into effective community-based rehabilitation programs. A current study is determining the functional, physiological, and metabolic changes in men and women who fracture a hip.
- The **University of Texas OAIC's** research focuses on age-related sarcopenia, a progressive loss of muscle mass that leads to muscle weakness, limited mobility, and increased susceptibility to injury, and the contribution of sarcopenia to loss of independence in older persons. OAIC researchers have identified protein changes in upper leg muscles associated with hemiparetic stroke (affecting one side of the body). Other studies are assessing the effects of bed rest on muscle function. New technologies under development at the University of Texas OAIC will make it easier to identify damaged proteins in aged tissues, which will help scientists understand the effects of aging on muscle function.
- The **Wake Forest University OAIC's** mission is to assess the risk factors of physical disability in older adults and to develop and test effective prevention therapies. The Cooperative Lifestyle Intervention Program is an 18-month randomized, controlled trial to assess the effectiveness of physical activity, with and without weight loss, in the treatment of mobility disability. The 288 participants are older, overweight, or obese men and women who have cardiovascular disease or metabolic syndrome (a group of medical problems that increase heart disease and diabetes risk).
- The **Yale University Center OAIC's** research theme is the investigation of geriatric health conditions that have several causes. This focus includes single conditions resulting from several contributing factors or affecting several outcomes, and multiple conditions occurring at the same time. One study area is falls among the elderly. The Yale

Precipitating Events Project includes monthly assessments of participants' functional status over 10 years. In a landmark clinical trial, investigators from the Yale OAIC demonstrated that functional decline among frail older persons can be prevented through a prehabilitation program targeting underlying impairments in physical capabilities. Future research by this group will develop and test two strategies to restore the ability of older persons living in the community to bathe themselves as well as develop approaches to preventing mobility disability.

In a landmark clinical trial, investigators from the Yale OAIC demonstrated that functional decline among frail older persons can be prevented through a prehabilitation program targeting underlying impairments in physical capabilities.

- The **University of Michigan Center OAIC,** the first OAIC funded by NIH, advances research on health care problems of older adults. One of the Michigan OAIC's projects is determining whether deficiencies of dopamine (a chemical brain messenger) in older people contribute to gait imbalance and falls. The study investigators hope to demonstrate that L-DOPA, an agent that is converted to dopamine in the brain, could be an effective treatment for older adults who are experiencing problems with walking and falls.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the OAICs

The OAIC Coordinating Center at Wake Forest University facilitates information exchange and research collaborations among OAICs. The Coordinating Center helps develop and implement projects in shared areas of interest. The Coordinating Center's major activities are coordinating and enhancing OAIC training programs and organizing seminars and other activities for trainees at the OAIC Annual Scientific Meeting.

Evaluation Plans

NIH program staff review the progress of each OAIC at the end of each award cycle, typically every 5 years. In addition, a panel of experts external to the OAICs conducts a formal mid-cycle review 2 to 3 years into the funding cycle of each center. This review assesses the OAIC's progress in meeting the goals in its application and identifies areas of concern to address prior to the next competing renewal. NIH staff provides a written summary of the review to each OAIC principal investigator for use in directing the center.

Future Directions

NIH plans to continue to fund new and existing Claude D. Pepper OAICs. Because the number of qualified applicants for OAIC sites continues to grow, a new OAIC site is planned by FY 2010, bringing the total number of OAIC sites to 12.

Table 4-2. Claude D. Pepper Older Americans Independence Centers (OAICs)

Institution and Location	Year Established
Duke University, Durham, NC	1955[14]
University of Michigan, Ann Arbor, MI	1989
University of California, Los Angeles, CA	1991
Wake Forest University, Winston-Salem, NC	1991[15]
Yale University, New Haven, CT	1992
University of Maryland, Baltimore, MD	1994

Claude D. Pepper Older Americans Independence Centers

Institution and Location	Year Established
University of Texas Medical Branch, Galveston, TX	1999
Johns Hopkins University, Baltimore, MD	2003
University of Pittsburgh, Pittsburgh, PA	2004
University of Florida, Gainesville, FL	2007
Boston University, Boston, MA	2008

[8] Federal Interagency Forum on Aging Related Statistics. Older Americans 2008: Key Indicators of Well-Being. Washington, DC: Federal Interagency on Aging-Related Statistics; 2008.
[9] For more information, see *MMWR Morb Mortal Wkly Rep* 2006;55(40):1089-92. PMID: 17035926.
[10] For more information, see http://www.nof.org/advocacy/prevalence/index.htm.
[11] U.S. Department of Health and Human Services. 65+ in the United States: 2005, Current Population Reports, Special Studies. U.S. Department of Health and Human Services/NIH/NIA and the U.S. Department of Commerce/Economics and Statistics Administration/U.S. Census Bureau: December 2005.
[12] For more information, see http://www.cdc.gov/nchs/products/pubs/pubd/hus/healthexpenditures.htm.
[13] Spillman BC, Lubitz J. *N Engl J Med* 2000;342:1409-15, PMID: 10805827; Feder J, et al. *Health Aff* 2000;19:40-56,.PMID: 10812780.
[14] The only remaining Geriatric Research and Training Center.
[15] NIH added a Coordinating Center to the OAIC program in 2005 to promote scientific collaborations among Pepper Center investigators and to facilitate the sharing of unique resources across all sites. The Coordinating Center is currently located at Wake Forest University.

Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

Overview

Why the Wellstone MDCRCs Were Established

The Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (the MD-CARE Act, Pub, L. No. 107-84) included provisions for expanding and intensifying research on muscular dystrophy and mandated that NIH establish Centers of Excellence for muscular dystrophy research. Congress designated the centers as the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (Wellstone MDCRCs) in the Omnibus Appropriations for FY 2004 (Public Law 108-199) in honor of the former Minnesota senator who was a driving force behind the MD-CARE Act. The MD-CARE Act of 2008 officially renamed the centers.

How the Wellstone MDCRCs Function within the NIH Framework

NIAMS, NINDS, and NICHD fund the Wellstone MDCRCs through the U54 Specialized Centers Cooperative Agreement award mechanism (see Table 4-3). NHLBI also has co-sponsored the two most recent competitions for Wellstone MDCRCs and plans to support projects within future Wellstone MDCRCs if NIH receives fundable applications that address NHLBI's mission.

A Steering Committee, consisting of directors and co-directors of each center and NIH science officers, coordinates the Wellstone MDCRCs' scientific program. Through annual meetings and regular conference calls, the Steering Committee promotes collaborations among center investigators and makes strategic decisions about Wellstone MDCRC goals and activities, including standardization of operating procedures.

Description of Disease or Condition

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of skeletal muscles. Many dystrophies also affect other organ systems such as the heart, blood vessels, and gastrointestinal tract (stomach and intestines). Some forms occur in infancy or childhood, whereas others usually do not appear until middle age or later. The Wellstone MDCRCs address, but are not limited to, the following conditions.

- **Duchenne and Becker Muscular Dystrophies**. Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy. An X-linked recessive disease (related to genes carried on the X chromosome), it primarily affects males who inherit a genetic mutation from their mothers. Boys who have DMD lack the protein dystrophin, which muscle cells need to function properly. DMD usually becomes evident when a child begins walking. Patients typically require a wheelchair by age 10 to 12 and die in their late teens or 20s. Becker muscular dystrophy (BMD), a less severe disease, occurs when the body produces a form of dystrophin that does not work properly.
- **Myotonic Dystrophy**. Myotonic dystrophy is the most common adult form of muscular dystrophy, although forms of this disease can affect newborns and other children. It is marked by myotonia (an inability to relax muscles after they contract) and muscle wasting and weakness. Myotonic dystrophy varies in severity and symptoms. It can affect body systems in addition to skeletal muscles, including the heart, endocrine organs (organs that release hormones, or substances that affect cell function in another part of the body, into the bloodstream), eyes, and gastrointestinal tract.
- **Facioscapulohumeral Muscular Dystrophy (FSHD).** FSHD initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humeral). Symptoms usually develop in the teenage years. Some affected individuals become severely disabled. Wasting of muscles of the trunk can lead to life-threatening breathing complications.

- **Limb-Girdle Muscular Dystrophies (LGMDs).** All LGMDs show a similar distribution of muscle weakness, affecting both upper arms and legs. Scientists have identified many forms of LGMDs; some affect children, whereas others affect adults.
- **Miyoshi Myopathy.** Miyoshi myopathy causes initial weakness in the calf muscles. It is caused by defects in the same gene that is responsible for one form of LGMD, suggesting that research progress against one form of muscular dystrophy could lead to a better understanding of other forms as well.

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Treatments such as physical therapy, use of appliances for support, corrective orthopedic surgery, and drugs can reduce symptoms and improve quality of life for some individuals. Some drugs, such as corticosteroids, can slow the progression of DMD to some extent but have adverse effects. Several treatments, including gene therapy, cell-based treatments, and strategies to reduce muscle wasting have shown promise in experiments using cells and animals. Clinical trials of some therapies have begun, including the use of drugs to reduce muscle damage, approaches to increase muscle mass by stopping the activity of other proteins that inhibit muscle growth, and strategies to bypass mutations that cause disease.

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy.

Burden of Illness

DMD and BMD affect 1 in 3,500 to 1 in 5,000 boys. With more than 4 million annual births in the United States, about 400 to 600 boys are born with DMD or BMD every year.[16] Myotonic dystrophy affects approximately 1 in 8,000 people worldwide,[17] whereas FSHD affects approximately 1 in 20,000 people and affects men and women equally.[18]

The MD-CARE Act called for the Centers for Disease Control and Prevention (CDC) to collect and analyze information on the number, incidence, correlates, and symptoms of individuals with muscular dystrophy. Recently published results from the project described the delay between the start of symptoms and definitive diagnosis of DMD.[19]

Scope of NIH Activities: Research and Programmatic

As nationally recognized Centers of Excellence in muscular dystrophy, the Wellstone MDCRCs promote communication and collaboration, develop and share research resources, and help train new muscular dystrophy researchers. Each center can conduct a mixture of basic research to understand the diseases, translational research to turn basic research findings into interventions for patients, and clinical studies to test interventions in people. The overall focus of the Wellstone MDCRCs is to integrate activities to develop therapies for muscular dystrophies. In 2008, NIH funded two new Wellstone MDCRCs and renewed one that had received funds from the original competition in FY 2003.

Collectively, the Wellstone MDCRCs conduct research on various forms of muscular dystrophy, including some not listed above. Examples of research topics addressed by the Wellstone MDCRCs in FY 2008 and FY 2009 follow.

- The **University of Pittsburgh** center, for which funding ended in FY 2009, focused on developing gene therapy techniques, as well as research on muscle stem cells as potential therapies for DMD.
- At the **University of Rochester** center, researchers are examining cellular and molecular factors that contribute to myotonic dystrophy and testing potential treatments.
- The **University of Washington** center, for which funding ended in 2009, focused on developing gene therapy techniques for DMD and studying the processes that lead to FSHD.
- Ongoing research at the **Children's National Medical Center** focuses on genetic and cellular factors that contribute to DMD's progression and patient responses to treatment.
- Research at the **University of Iowa** center focuses on gene and stem cell treatments for DMD, LGMDs, and other muscular dystrophies.

- Ongoing research at the **University of Pennsylvania** and **Johns Hopkins University** center focuses on improving muscle growth or slowing muscle deterioration. In the future, researchers may be able to use these approaches to treat several kinds of muscular dystrophies and other disorders.
- Established in FY 2008, the **Boston Biomedical Research Institute** center seeks to identify biomarkers and is conducting a clinical trial of a potential FSHD therapy. In FY 2009, the center received funding through the American Recovery and Reinvestment Act of 2009 (ARRA) to accelerate collection and study of multiple biopsies.
- Established in FY 2008, the **University of North Carolina at Chapel Hill** center is developing and testing gene therapies for DMD and other muscle disorders.

Each Wellstone MDCRC has core facilities that provide unique resources or services for the muscular dystrophy research community. Cores include repositories of research data and biologic resources from patients with different types of muscular dystrophy, assistance with gene therapy development and production, and a data-coordinating site for clinical trials conducted by the Cooperative International Neuromuscular Research Group (CINRG). The Wellstone MDCRC program also contributes to therapy development by supporting the National Center for Canine Models of Duchenne Muscular Dystrophy and a facility at the University of Pennsylvania that tests mice for muscular dystrophy investigators.

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the Wellstone MDCRC program was $9.9 million in FY 2008 and $9.3 million in FY 2009, including $406,000 from ARRA funds.

FY 2008 and FY 2009 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments in FY 2008 and FY 2009 include establishing new Wellstone MDCRCs at the Boston Biomedical Research Institute and the University of North Carolina at Chapel Hill in FY 2008. In addition, the Wellstone MDCRC at the University of Rochester competed successfully for renewal through FY 2013. The two other centers funded under the first Wellstone competition (University of Pittsburgh and University of Washington) ended their formal center programs in FY 2009. However, many of these centers' investigators continue to conduct muscular dystrophy research with support from other grants. Moreover, these universities still are eligible to compete for future Wellstone MDCRC grants.

In 2005 and 2006, NIH invited junior investigators from the Wellstone MDCRCs to apply for Wellstone fellowships, which support salary and some research expenses.[20] In FY 2008 and FY 2009, fellowship recipients published articles in high-quality journals; one left the center to establish a muscular dystrophy research program at a new institution; and another received an independent NIH research grant. Because training and career development is an important component of the Wellstone MDCRC program, all centers funded under the Wellstone MDCRC FY 2008 or FY 2010 competition will have formal training and education core facilities. These facilities will provide stipends to predoctoral and postdoctoral researchers and enhance the programs' educational environments.

Because training and career development is an important component of the Wellstone MDCRC program, all centers funded under the Wellstone MDCRC FY 2008 or FY 2010 competition will have formal training and education core facilities.

The Wellstone MDCRC program has enhanced public-private partnerships in muscular dystrophy. Projects have involved collaborations with, and additional support from, companies such as PTC Therapeutics, Acceleron Pharma, and Insmed. The centers also have strong ties with patient advocacy groups, including the Muscular Dystrophy Association, Parent Project MD, the FSH Society, Inc., the Jain Foundation, and the Foundation to Eradicate Duchenne, Inc. These organizations provide additional support for center research projects. The synergy created by NIH resources and the involvement of industry and advocacy groups is accelerating progress toward muscular dystrophy treatments.

In FY 2008, the NIH Wellstone MDCRC program, the NIH Office of Rare Diseases, the Foundation to Eradicate Duchenne, Inc., and the European organization TREAT-NMD hosted two workshops.[21] The goal of these workshops was to develop standard protocols for DMD treatment studies in mice and dogs. By adopting standardized protocols, investigators will be better able to compare results from different studies. Moreover, the outcomes will greatly accelerate treatment testing in animals.

The Wellstone MDCRC core facilities are national resources for the muscular dystrophy community. These facilities have been publicized at national meetings and through center websites and the Wellstone MDCRC website. These shared research tools foster collaborations across departments or schools within institutions and among investigators and health care providers nationwide. Examples of these facilities follow.

- The University of Rochester established the **Repository and National Registry of Myotonic Dystrophy Patients and Family Members** when NIH renewed the center's funding in FY 2008. The facility, a combination of the center's existing Tissue Repository Core and the NIH-funded Registry of Myotonic Dystrophy Patients and Family Members, provides researchers with cell or tissue samples and clinical information about the donors of these samples. This resource has facilitated two publications in 2008, advancing understanding of sleep disturbances[22] and chronic pain[23] in these patients.
- The University of Iowa's **Muscle Tissue/Cell Culture/Diagnostics Core** maintains a muscle tissue repository of well-characterized samples from a spectrum of muscular dystrophy types. The core continues to expand its repertoire of diagnostic services that are not readily available through clinical laboratories. Accomplishments in 2009 include contributions to a genetic test for a mutation associated with congenital muscular dystrophy in the Ashkenazi Jewish population.[24]
- The MDCRC at the University of North Carolina at Chapel Hill launched the **National Vector Muscular Dystrophy Core** in FY 2008. The Core is producing and testing gene therapy materials for researchers.[25] As tests are completed successfully, the facility will supply investigators with materials that they can use for clinical research. The core also will help investigators submit documents to regulatory agencies (such as the U.S. Food and Drug Administration) and comply with all relevant regulations. In FY 2009, the center successfully competed for supplemental ARRA funding to purchase additional laboratory equipment.
- The **Physiological Assessment Core** at the University of Pennsylvania evaluates muscle integrity and function for center investigators and other academic and industrial researchers. The facility's experienced staff conduct measurements that now are the standard for showing whether a new treatment is effective in animals. Accomplishments in FY 2008 and 2009 include contributions to papers on muscle function in models of FSHD[26] and DMD.[27]

Research Activities and Outcomes

The Wellstone MDCRCs conduct basic, translational, and clinical studies related to a variety of muscular dystrophies. Examples of accomplishments in FYs 2008 and 2009 are provided below.

- Investigators at the Nationwide Children's Hospital (Columbus, Ohio), funded through a subcontract from the University of Pittsburgh Wellstone MDCRC, developed a gene-therapy technique for making alpha-sarcoglycan protein (which is essential for muscle function) without triggering a destructive response by the body's immune system. The three-person clinical trial builds on findings from the University of Iowa and elsewhere showing that restoring alpha-sarcoglycan gene expression can halt the advance of a type of limb-girdle muscular dystrophy in mice.[28] The Nationwide Children's Hospital study demonstrated that the gene-delivery strategy was safe and that a single injection produced gene expression for at least 12 weeks.[29] Although the study was designed to test safety (not improvements in muscle function), findings from one patient suggest that the delivered gene might be useful for restoring muscle function.
- Animal study findings from Wellstone MDCRCs have suggested strategies for people who have various muscular dystrophies. For example, mouse studies at the University of Pennsylvania and Johns Hopkins University Wellstone MDCRC showed that a drug being studied for hepatitis C treatment slowed progression of congenital muscular dystrophy, DMD, and LGMDs by blocking damage caused by calcium to mitochondria (the main energy sources of

cells).[30] Although the drug might not be appropriate for people because of its potential side effects, the study shows that protecting cells from calcium damage could be beneficial.

- Researchers at the Children's National Medical Center increased the amounts of modified dystrophin protein in dogs with DMD, a disease caused by the body's inability to make dystrophin protein. They used artificial molecules (morpholino oligonucleotides) that cause the cell's protein-generating machinery to skip over the damaged segment of the dystrophin gene and produce shortened, but functional, dystrophin. If researchers can refine this strategy so that it can safely be studied in people, this approach could benefit nearly 90 percent of patients with DMD.[31]

Some researchers are exploring the role of neuronal nitric oxide synthase in controlling blood flow in skeletal muscle and thus in minimizing the fatigue associated with exercise that many people with a nerve or muscle disease experience.

- Wellstone MDCRC researchers are using animals to find treatments that could be effective for several different types of muscular dystrophies. Some researchers are exploring the role of neuronal nitric oxide synthase (nNOS) in controlling blood flow in skeletal muscle and thus in minimizing the fatigue associated with exercise that many people with a nerve or muscle disease experience.[32] University of Iowa scientists used mice with DMD to show that a drug that allows blood vessels to dilate prevents the severe fatigue that the mice experienced after brief exercise periods. Other studies by researchers at the University of Missouri in collaboration with an investigator at the Seattle Wellstone Center restored functioning of diseased mice to nearly normal levels by using a gene therapy strategy involving nNOS.[33]

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the Wellstone MDCRCs

In response to research advances and Steering Committee recommendations, NIH changed the requirements for FY 2008[34] applicants to improve the program's overall effectiveness, efficiency, and outcomes. The FY 2008 solicitation emphasized multidisciplinary teams and patient-oriented research. Details about the recommendations' rationale and implementation follow.

- NIH removed the requirement that all centers conduct basic research on disease mechanisms because the number of findings that are ready to be studied in animals or humans has increased dramatically since the last competitions.[35, 36] This change allows the Wellstone MDCRCs to focus more on translating basic findings to human studies and conducting studies in humans. Meanwhile, NIH continues to encourage basic muscular dystrophy research through other funding mechanisms, such as traditional research project grants.
- By reducing the required number of projects from three to one, NIH allowed FY 2008 applicants to propose collaborative studies involving animal models of disease or human subjects that were larger, more expensive, and more in-depth than were possible under the original structure.
- NIH urged FY 2008 applicants to propose collaborative studies that address at least one gap in muscular dystrophy treatment research and overcome obstacles in the development of therapies.
- In FY 2008, all applicants had to provide letters from other researchers to show how one of their proposed cores would fill a high-priority need beyond their individual institutions. This change was designed to increase the Wellstone MDCRC program's ability to serve the entire muscular dystrophy research community.
- NIH enhanced the program's training activities in FY 2008 by requiring all centers to create Research Training and Education Cores that support predoctoral students and postdoctoral fellows. The addition of a formal career-development program at each site enhances the Wellstone MDCRCs' contributions to the pipeline of new muscular dystrophy researchers.
- Engaging patients throughout the research process can improve a program's impact by ensuring that researchers are developing and testing treatments that are acceptable to patients (and the parents of pediatric patients). To this end, the new Wellstone MDCRC at the Boston Biomedical Research Institute has been working closely with the FSH Society to jointly set and achieve research objectives with the patient community.
- NIH is organizing a broader collaborative network of muscular dystrophy researchers. To make communication more seamless among everyone who cares about people with muscular dystrophy and to increase the exchange of

knowledge for treatment development, NIH invited major advocacy groups and grantees who have other center awards to participate in a 2009 meeting of the Wellstone MDCRCs. Investigators presented examples of collaborations among the centers and other researchers. New opportunities for interactions and multi-laboratory projects were identified.

Evaluation Plans

Major review criteria for the Wellstone MDCRCs include the degree to which an institution shows that it can foster substantive collaborations among its researchers and with scientists elsewhere that address key issues in muscular dystrophy and its potential to serve as a national infrastructure and training resource.

NIH responded to the burgeoning number of basic research findings in muscular dystrophy by changing the focus of the FY 2008 Wellstone MDCRC competition to encourage research that translates basic findings about the disease to human studies and applications in the clinic.

NIH responded to the burgeoning number of basic research findings in muscular dystrophy by changing the focus of the FY 2008 Wellstone MDCRC competition to encourage research that translates basic findings about the disease to human studies and applications in the clinic. Informal comments about the change in focus from reviewers, grantees, and advocacy groups were positive. Discussions about the centers' structure among NIH program staff and IC directors led to a decision to retain the structure adopted for the FY 2008 competition. NIH will continue to monitor the program's coordination and productivity as staff review the progress of each center at the time of noncompeting renewal and through regular contact with Wellstone MDCRC leaders through the Steering Committee.

Future Directions

NIH is committed to supporting six outstanding Wellstone MDCRCs. The agency issued 3 5-year awards to the Wellstone MDCRC program in FY 2008. In FY 2010, NIH is holding an open competition and intends to fund up to three other center sites.[37] Grantees will join the network of Wellstone MDCRCs to translate scientific findings and technological developments into treatments for muscular dystrophies.

NIH supports multi-project grants and core centers for muscular dystrophy research at academic institutions in addition to the Wellstone Centers. The agency also is promoting interactions among investigators at the Wellstone Centers and these other institutions to expand the scope and strength of the Wellstone Network. For example, the Wellstone Center meeting in June 2009 included participants from two NIAMS-funded core centers, two NINDS-supported program project grants, the NINDS- and NIAMS-supported National Center for Canine Models of DMD, and representatives from patient advocacy groups.

Table 4-3. Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs)

Institution and Location	Year Established
University of Pittsburgh, Pittsburgh, PA	2003
University of Rochester, Rochester, NY	2003
University of Washington, Seattle, WA	2003
Children's National Medical Center, Washington, DC	2005
University of Iowa, Iowa City, IA	2005

Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

Institution and Location	Year Established
University of Pennsylvania, Philadelphia, PA, and Johns Hopkins University, Baltimore, MD	2005
Boston Biomedical Research Institute, Boston, MA	2008
University of North Carolina, Chapel Hill, NC	2008

[16] For more information, see www.cdc.gov/ncbddd/duchenne/who.htm.
[17] For more information, see http://ghr.nlm.nih.gov/condition=myotonicdystrophy.
[18] For more information, see www.nlm.nih.gov/medlineplus/ency/article/000707.htm.
[19] Ciafaloni E, et al. *J Pediatr* 2009;155(3):380-5. PMID: 19394035.
[20] For more information, see http://grants2.nih.gov/grants/guide/notice-files/NOT-AR-05-001.html.
[21] Nagaraju K, et al. *Neuromuscul Disord* 2009;19(7):502-6. PMID: 19560356. PMCID: PMC2766092.
[22] Ciafaloni E, et al. *Neurology* 2008;70(3):226-30. PMID: 18195268.
[23] Jensen MP, et al. *Arch Phys Med Rehabil* 2008;89(2):320-8. PMID: 18226657.
[24] Chung W, et al. *Prenat Diagn* 2009;29(6):560-9. PMID: 19266496. PMCID: PMC2735827.
[25] Li C, et al. *J Virol* 2009;83(13):6817-24. PMID: 19369348. PMCID: PMC2698563.
[26] Daniels DW, et al. *Arch Oral Biol* 2008;53(2):187-92. PMID: 18028868. PMCID: PMC2262833.
[27] Millay DP, et al. *Nat Med* 2008;14(4):442-7. PMID: 18345011. PMCID: PMC2655270.
[28] Pacak CA, et al. *Mol Ther* 2007;15(10):1775-81. PMID: 17653106.
[29] Mendell JR, et al. *Ann Neurol* 2009; 66(3):267-70. PMID: 19798725.
[30] Millay DP, et al. *Nat Med* 2008;14(4):442-7. PMID: 18345011. PMCID: PMC2655270.
[31] Millay DP, et al. *Nat Med* 2008;14(4):442-7. PMID: 18345011. PMCID: PMC2655270.
[32] Yokota T, et al. *Ann Neurol* 2008;456(7221):511-5. PMID: 18953332. PMCID: PMC2588643.
[33] Lai Y, et al. *Clin Invest* 2009;119(3):624-35. PMID: 19229108. PMCID: PMC2648692.
[34] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-08-002.html.
[35] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-03-001.html.
[36] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-04-008.html.
[37] For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-027.html.

National Center on Minority Health and Health Disparities Centers of Excellence Program

Overview

NIH defines health disparities as differences in the incidence, prevalence, morbidity, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups.[38] These population groups are African Americans, American Indians, Alaska Natives, Asian Americans, Hispanic Americans, Native Hawaiians, and Pacific Islanders, subpopulations of all of these racial/ethnic groups, socioeconomically disadvantaged individuals, and medically underserved populations including individuals residing in rural and urban areas.

The National Center on Minority Health and Health Disparities (NCMHD) Centers of Excellence (COE) program is one of several programs that are central to NIH's scientific investment strategy for addressing and ultimately eliminating health disparities (see Table 4-4). That strategy encompasses:

- Conducting and supporting basic, clinical, social sciences, and behavioral research
- Promoting research infrastructure and training
- Fostering emerging programs
- Disseminating information
- Reaching out to racial and ethnic minority and other communities that experience health disparities

Why the NCMHD Centers of Excellence Were Established

The Minority Health and Health Disparities Research and Education Act of 2000 (Pub. L. No. 106-525) included provisions for the creation of NCMHD to conduct and support research, training, and dissemination of information with respect to minority health conditions and other populations with health disparities. Section 485F specifically mandated that NCMHD establish Centers of Excellence in research institutions for the purpose of conducting biomedical and behavioral health disparities research and training.

How the NCMHD Centers of Excellence Function within the NIH Framework

NCMHD established COEs to create a comprehensive platform in academic institutions to address health disparities in priority diseases and conditions through the fundamental strategies of research, training a diverse scientific workforce, and engagement of the community. NCMHD also designed the COE program to support Department of Health and Human Services initiatives for eliminating health disparities.

Since 2002, NCMHD has established Centers of Excellence (COEs) in 32 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. NCMHD supported 49 COEs in FY 2008 and 51 COEs in FY 2009.

Since 2002, NCMHD has established COEs in 32 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. Initially, the program used three different funding mechanisms for Resource-Related Centers (R-24), Exploratory Centers (P20), and Comprehensive Centers (P60). The use of these different funding mechanisms allowed NCMHD to support institutions with varying levels in biomedical research expertise and capacity. This approach also enabled NCMHD to leverage resources to support the capabilities of the Nation's geographically and culturally diverse institutions that have longstanding partnerships with local and regional health disparity organizations and communities. The Resource-Related Centers mechanism, which NCMHD no longer uses, enabled institutions with emerging or modest research infrastructures to begin building research capacity to address health disparities. Several institutions that received these R24 awards have since successfully established an NCMHD COE using the Exploratory Centers mechanism.

Similar to other COEs that NIH supports through these mechanisms, a typical project period is 4 to 5 years. All NCMHD COEs (P20 and P60) established since FY 2005 have had project periods of 5 years.

Currently, the types of institutions funded directly by the NCMHD COE program or through partnerships with NCMHD COEs are broad. These institutions include research-intensive institutions, medical schools, historically black colleges and universities, Hispanic-serving institutions, tribal colleges/universities, and liberal arts colleges. NCMHD supported 49 COEs in FY 2008 and 51 COEs in FY 2009.

As a hub for health disparities research, NCMHD COEs provide opportunities for the development of novel partnerships between different types of institutions, such as community-based organizations or foundations, to partner in the conduct of rigorous basic scientific research, human subjects and vertebrate animal research, and applied population and community-based research.

One example of an NCMHD COE is the partnership funded in FY 2009 that established the University of South Florida and Moffitt Transdisciplinary Center to Address Cancer Health Disparities. Florida has the second highest estimated number of new cancer cases and cancer deaths. This COE seeks to reduce racial and ethnic cancer disparities through research, education, training, and community engagement. Significantly, this partnership will engage three different communities by conducting community cancer discussion groups, health and science fairs, and workshops, and by using social marketing approaches to disseminate information through radio talk shows, an interactive website, a Facebook page, and podcasts. The Florida program also provides opportunities for increasing the pool of investigators from populations that experience health disparities through research training, faculty development, programs and activities to interest K-12 students in science, health information dissemination, and approaches to increasing the participation of these populations in clinical trials.

Description of Disease or Condition

The research and other COE activities that NCMHD supports are not limited to or focused on a single disease, illness, or condition. As described in various solicitations published in the *NIH Guide for Grants and Contracts*, the NCMHD COEs conduct research on health disparities associated with the following priority diseases and conditions: cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity. The NCMHD COE program also supports research on lung disease, liver disease, psoriasis, scleroderma, and glomerular (kidney) injury; all of these diseases and conditions disproportionately affect racial and ethnic minorities.

NCMHD Centers of Excellence conduct research on health disparities associated with the following priority diseases and conditions: cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity. The program also supports research on lung disease, liver disease, psoriasis, scleroderma, and glomerular (kidney) injury; all of these diseases and conditions disproportionately affect racial and ethnic minorities.

Burden of Illness

The diversity of the contemporary American population is one of the Nation's greatest assets. However, the richness of this diversity is diminished by the disproportionate burden of disease and illness and the reduced access to quality health care that racial and ethnic minority populations and the rural and urban poor experience. Compelling evidence of the disparate health status of America's racial and ethnic minority and economically disadvantaged populations includes their shorter life expectancies and higher rates of cancer, birth defects, infant mortality, asthma, diabetes, obesity, cardiovascular disease, and stroke. Racial and ethnic minorities and the medically underserved also suffer a disproportionate burden of morbidity and mortality associated with HIV/AIDS; autoimmune diseases, such as lupus and scleroderma; oral health; sexually transmitted diseases; mental disorders; violence; and substance abuse.

Recent statistics on disparities for select diseases and conditions are provided in the following tables.

Ischemic Stroke Death Rates[39]	
Race/Ethnicity	***Rate (per 100,000)***
White	73.7
African American	95.8
American Indian/Alaska Native	48.6
Asian/Pacific Islander	45.8
Hispanic	39.7

Intracerebral Stroke Death Rates[40]	
Race/Ethnicity	***Rate (per 100,000)***
White	13.2
African American	22.5
Asian/Pacific Islander	20.1
American Indian/Alaska Native	10.4
Hispanic	12.0

Breast Cancer Death Rates by Race/Ethnicity, 2002—2006[41]	
Race/Ethnicity	***Rate (per 100,000 Women)***
All Races	24.5
White	23.9
African American	33.0
Asian/Pacific Islander	12.5
American Indian/Alaska Native	17.6
Hispanic	15.5

Prostate Cancer Rates by Race/Ethnicity, 2002—2006[42]	
Race/Ethnicity	***Rate (per 100,000 Men)***
All Races	25.6
White	23.6
African American	56.3
Asian/Pacific Islander	10.6
American Indian/Alaska Native	20.0
Hispanic	19.6

Obesity in Men, 2003—2006[43]	
Group	***Percent***
All	33.1
White	33.0
African American	36.3
Mexican	30.4

Obesity in Women, 2003—2006[44]	
Group	***Percent***
All	35.2
White	32.5
African American	54.3
Mexican	42.6

Scope of NIH Activities: Research and Programmatic

The scope of activities at NCMHD COEs are guided by the Research, Infrastructure, and Outreach (RIO) framework used in developing the NIH Health Disparities Strategic Plan. Implementing the RIO framework within the NCMHD COE program provides a flexible structure that allows considerable freedom in designing and implementing the multi- and transdisciplinary strategies, studies, interventions, and activities required for reducing and ultimately eliminating health disparities.

National Center on Minority Health and Health Disparities Centers of Excellence Program

The NCMHD COE program requires all COEs to establish mandatory cores:

- An Administrative Core for carrying out and overseeing administrative matters and functions
- A Research Core for conducting, coordinating, generating, and advancing research on health disparities
- A Research Training and Education Core for conducting and advancing research training
- A Community Engagement Core for engaging communities and others as partners in eliminating health disparities through community participation in research and the joint development and dissemination of effective health information messages and research findings

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the NCMHD COE program was $56.8 million in FY 2008, and $72.5 million in FY 2009,[45] including $5.6 million from ARRA funds.

FY 2008 and FY 2009 Progress Report

Significant programmatic accomplishments include establishing seven new COEs and one competing renewal (see Table 4-4). The number of active NCMHD COEs was 49 in FY 2008 and 51 in FY 2009.

The COE at the University of Southern California received one of three telehealth/telemedicine supplements to develop technology and tools for use with mobile devices to prevent pediatric obesity among Hispanic and African American youth in Los Angeles.

Administrative supplements were made in FY 2008 to NCMHD COEs to support the following:

- The use of telehealth and telemedicine. NCMHD considers the use of telehealth and telemedicine to be innovative strategies to reduce and eliminate health disparities in hard-to-reach rural, Alaska Native, American Indian, Native Hawaiian, Pacific Islander, African American, Hispanic American, or Asian American populations.
- Regional seminar series on health disparities to share and disseminate minority health and health disparities research findings and increase the participation of health professionals and community stakeholders in the effort to eliminate health disparities.
- The development and implementation of science education programs for grades K–12 to promote careers in biomedical, behavioral, and biosocial research for populations that are underrepresented in the health science fields.

Research Activities and Outcomes

Funding for the NCMHD COEs has resulted in several FY 2008 and FY 2009 research accomplishments. The centers conduct research on minority health and the biologic and non-biologic factors contributing to health disparities. As shown by the following examples, NCMHD researchers are exploring the role of social and cultural factors in the prevalence of priority diseases and conditions.

The Carolina-Shaw Partnership for the Elimination of Health Disparities completed a pilot study to qualitatively explore cultural attitudes and perceptions toward body image, food, and physical activity among a sample of overweight African American girls.[46] The investigators found that weight and body size preferences were determined primarily by the individual and her immediate social circle and were less influenced by opinions of those outside of the social circle. The findings also showed that the girls' food choices depended on texture, taste, appearance, and context more than nutritional value; engagement in recreational physical activity was influenced by time constraints from school and extracurricular activities and by neighborhood safety; participation in structured exercise was limited because of the cost and time required to maintain personal aesthetics (hair and nails); and the girls did not perceive celebrities as role models for diet and physical activity habits.

The University of Oklahoma Center for American Indian Diabetes Health Disparities seeks to reduce and eventually eliminate the excess mortality, morbidity, and loss of quality of life and culture due to diabetes.

The University of Oklahoma Center for American Indian Diabetes Health Disparities seeks to reduce and eventually eliminate the excess mortality, morbidity, and quality of life and culture lost due to diabetes. The center also focuses on maternal health, infant mortality, and obesity. Current studies include Early Markers of Pre-eclampsia in American Indians with Type 2 Diabetes, Insulin Resistance and Glucocorticoid Treatment of Inflammatory Diseases of High Prevalence among American Indians, and American Indian Diabetes Beliefs and Practices: Maternal Care, Infant Mortality, and Adherence. In addition, the center is providing instruction and support for conducting practical research to address diabetes within their health care settings to a cadre of nurses from American Indian clinics and hospitals in Oklahoma and Kansas. The Community Engagement/Outreach Core supports the Native Youth Preventing Diabetes summer camp that is open to all Oklahoma American Indians ages 8 to 12 years.

The Uniform Services University Center for Health Disparities Research, a partnership between the Uniform Services University of the Health Sciences and the University of Maryland, Eastern Shore, is conducting research on long-term behavioral modification to reduce and prevent obesity among African American women. The center is using the results of this research to build a program on cardiovascular disease and metabolic syndrome, which disproportionately affect minority populations. The center's research addresses issues related to lifestyle and health, health care access, health status, and health disparities. The Healthy Lifestyles among African American Women through Weight Loss and Exercise project is exploring ways for women in faith-based communities to sustain weight reduction and maintenance efforts using different exercise regimes and behavioral therapies. The project's long-term goal is to decrease the risk and incidence of obesity and associated conditions.

The Uniform Services University Center for Health Disparities Research is using the results of its research on long-term behavioral modification to reduce and prevent obesity to build a program on cardiovascular disease and metabolic syndrome, which disproportionately affect minority populations.

Researchers at the Center for Research on Minority Health of the University of Texas M.D. Anderson Cancer Center and Prairie View A&M University are defining the biological relevance of susceptibility gene polymorphisms (different forms of these genes) as risk factors for cancer and other adverse health effects. Specifically, the researchers are developing and validating a food frequency questionnaire to assess the folate and vitamin B12 intake of Mexican American children in Texas. The study's short-term goal is to estimate the prevalence of the social, environmental, and genetic factors associated with stomach cancer risk among Mexican American children; the long-term goal is to prevent stomach cancer in Mexican Americans. The findings from this study could reduce stomach cancer health disparities in the United States and around the world.

To address the disproportionate burden and impact of HIV/AIDS on women of color, the University of Miami COE is evaluating the efficacy of an HIV risk reduction intervention delivered by Hispanic women. The intervention is culturally tailored to meet the needs of Hispanic women, who are disproportionally affected by HIV/AIDS. The intervention is designed to increase HIV prevention behaviors in inner-city Hispanic women. The study also is exploring the role of acculturation, family, stress, and family functioning as risk factors, protective factors, or both in the prevention of HIV/AIDS among Hispanic women.[47]

To address the disproportionate burden and impact of HIV/AIDS on women of color, the University of Miami COE is evaluating the efficacy of an HIV risk reduction intervention delivered by Hispanic women and designed for Hispanic women in the United States.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the NCMHD COEs

Since their inception in year 2002, NCMHD COEs made progress toward the elimination of health disparities. However, much more needs to be done in designing and taking the critical steps needed to translate research findings to meaningful actions that will improve the quality of life experienced by those overburdened by health disparities. Efforts need to be more targeted toward interventions that work. Specifically, guidance will be provided to COEs to:

- Establish partnerships with other NIH-funded centers and programs, other Federal agencies, and others committed to eliminating health disparities as a way to maximize resources.
- Increase the diversity of the scientific workforce, especially the number of women and biomedical and behavioral scientists from racial/ethnic and other health disparity populations. Focused efforts are especially needed to increase the number of women scientists and researchers who: a) remain in the sciences beyond the terminal research or professional degree and beyond the postdoctoral or residency stage and who pursue basic or clinical research as a career; and b) serve in leadership and decision-making roles as members of scientific review panels or members of national advisory councils.
- Create opportunities for biomedical and behavioral scientists to work with social scientists, health services researchers, and other public health researchers to address more effectively the transdisciplinary challenges in health disparities elimination and prevention research.
- Enhance the Nation's research capacity to conduct health disparities research by expanding the research and training opportunities available.

NCMHD and its COEs cannot act alone—NCMHD actively seeks new partners and also encourages each NCMHD COE to establish partnerships with other NIH-funded centers and programs, other Federal agencies, and others committed to eliminating health disparities.

Evaluation Plans

NCMHD program staff evaluate the COEs' annual progress by examining each COE's published peer-reviewed articles, books, and book chapters; conferences sponsored and presentations given on health disparities; community engagement activities, such as health fairs and other forums for disseminating health-promotion materials; community participation in research and clinical trials (if applicable); training of junior faculty from health disparity populations, postdoctoral fellows, and graduate and undergraduate students; and K–12 educational efforts. This review ascertains the COE's progress in meeting the aims and objectives of the grant and may identify areas of concern that need to be addressed.

Future Directions

The NCMHD COE program will continue to intensify research efforts to reduce and eliminate health disparities, with an emphasis on sustaining current partnerships and establishing new ones. NCMHD expects that its COEs will discover new biomedical and behavioral knowledge for improving minority health and eliminating health disparities within and across the priority areas of cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity, as well as in lung and liver diseases, psoriasis, scleroderma, and glomerular injury. An important emphasis area is reducing co-morbidities in populations that experience health disparities.

The NIH Science of Eliminating Health Disparities Summit, held in December 2008, provided significant recommendations for future research themes for COEs. These include, but are not limited to:

- Support for infrastructure that involves community leaders in the design and conduct of clinical trials. Since infrastructures can cover a wide range of diseases, investigators should take advantage of already established systems to maximize resources.
- Support studies using multi-level and/or ecological approaches that take into consideration the interactions between variables that represent individual, family, community, and neighborhood characteristics.

- Support research on the broad social and political processes that lead to or ameliorate social disparities in health. In the same way as the genome has been mapped, the fundamental social determinants of health must be mapped in order to understand the social and political processes that must inform the development of effective interventions.
- Promote greater interdisciplinary training opportunities to evolve a new scientific approach that includes disseminating information, communicating, and capacity-building.

The COEs also will continue to develop new technologies for measuring the interactions between these various factors and new paradigms. The resulting new knowledge and technologies will lead to the development of bio-psychosocial and other interventions and strategies for improving minority health and eliminating health disparities.

Conducting population-based studies for reducing the incidence and prevalence of health disparities among individuals living in different geographical regions of the United States—especially the Mississippi Delta, Appalachia, the U.S.-Mexico border region, and tribal communities—will continue to be important.

The success of these and future research efforts by the NCMHD COEs will continue to depend, in part, on the development of improved methodological tools, measures, validated instruments, and novel research designs for disentangling the contribution to health disparities of biologic, behavioral, and social factors, and health policies and practices. Conducting population-based studies for reducing the incidence and prevalence of health disparities among individuals living in different geographical regions of the United States—especially the Mississippi Delta, Appalachia, the U.S.-Mexico border region, and tribal communities—will continue to be important. NCMHD will continue to support studies to eliminate or decrease the impact of factors, including natural disasters, that contribute to the excess risks, morbidity, and mortality associated with living in these regions.

Table 4-4. NCMHD Centers of Excellence Active in FY 2008 and FY 2009

Institution and Location	Year Established
Charles R. Drew University of Medicine & Science, Los Angeles, CA	2002
Howard University, Washington, DC	2002
Johns Hopkins University, Baltimore, MD	2002
Morehouse School of Medicine, Atlanta, GA*	2002
Mount Sinai School of Medicine of NYU, New York, NY	2002
North Carolina Central University, Durham, NC	2002
San Diego State University, San Diego, CA	2002
Tuskegee University, Tuskegee, AL*	2002
University of California, San Diego, CA	2002
University of Hawaii, Manoa, HI	2002
University of North Carolina, Chapel Hill, NC	2002
University of Pennsylvania, Philadelphia, PA*	2002
University of Pittsburgh, Pittsburgh, PA	2002

National Center on Minority Health and Health Disparities Centers of Excellence Program

Institution and Location	Year Established
Columbia University Health Sciences, New York, NY	2003
Meharry Medical College, Nashville, TN	2003
New York University School of Medicine, New York, NY	2003
Texas A&M University System, College Station, TX	2003
Uniformed Services University of the Health Sciences, Bethesda, MD	2003
University of Alabama, Birmingham, AL	2003
University of Arizona, Tucson, AZ*	2003
University of California, Davis, CA	2003
University of Colorado Denver and Health Sciences Center, Aurora, CO	2003
University of Maryland, Baltimore, MD*	2003
University of Oklahoma Health Sciences Center, Oklahoma City, OK	2003
University of Puerto Rico Medical Sciences, San Juan, PR	2003
University of Texas Health Sciences Center, Houston, TX	2003
University of Texas M.D. Anderson Cancer Center, Houston, TX	2003
Yeshiva University, New York, NY	2003
University of South Alabama, Mobile, AL	2004
University of the Virgin Islands, St. Thomas, VI	2004
Loma Linda University, Loma Linda, CA	2005
University of Connecticut, Storrs, CT	2005
University of North Texas Health Sciences Center, Fort Worth, TX	2005
University of South Carolina, Columbia, SC	2005
University of South Dakota, Vermillion, SD	2005
Arizona State University, Tempe, AZ	2007
Case Western Reserve University, Cleveland, OH	2007
Clark Atlanta University, Atlanta, GA	2007
Florida International University, Miami, FL	2007
Montana State University, Bozeman, MT	2007

Institution and Location	Year Established
University of Arkansas Medical Sciences, Little Rock, AR	2007
University of Massachusetts, Boston, MA	2007
University of Miami, Coral Gables, FL	2007
University of Michigan, Ann Arbor, MI	2007
University of North Carolina, Greensboro, NC	2007
University of Southern California, Los Angeles, CA	2007
University of Texas, El Paso, TX	2007
Virginia Commonwealth University, Richmond, VA	2007
Winston-Salem State University, Winston-Salem, NC	2007
Medical College of Georgia, Augusta, GA	2009
State University of Albany, Albany, NY	2009
University of Illinois, Chicago, IL	2009
University of Minnesota, Twin Cities, MN	2009
University of South Florida, Tampa, FL	2009
University of Wisconsin, Madison, WI	2009
Weill Medical College, Ithaca, NY	2009

*Center was active in FY 2008 but not FY 2009

[38] For more information, see http://www.ncmhd.nih.gov/our_programs/strategic/pubs/VolumeI_031003EDrev.pdf, p. 7.
[39] Ayala C, et al. *Am J Epidemiol* 2001;154:1057-63. PMID: 11724723.
[40] Ibid.
[41] For more information, see http://seer.cancer.gov/statfacts/html/breast.html?statfacts_page=breast.html&x=16&y=16.
[42] For more information, see http://seer.cancer.gov/statfacts/html/prost.html?statfacts_page=prost.html&x=18&y=17.
[43] For more information, see Table 75 at http://www.cdc.gov/nchs/data/hus/hus08.pdf.
[44] Ibid.
[45] The funding increase from FY 2008 to FY 2009 is due to the addition of seven new NCMHD COEs and one competing renewal.
[46] Boyington JE, et al. *Prev Chronic Dis* 2008;5(2):A36. PMID: 18341772. PMCID: PMC2396970.
[47] For more information, see http://elcentro.sonhs.miami.edu/research/full_research_studies.html.

Rare Diseases Clinical Research Network

Overview

Why the RDCRN Was Established

The need for centers of excellence for rare diseases research has been voiced for more than 20 years. A disease is defined as rare if fewer than 200,000 persons in the United States have it. Scientists have identified approximately 6,500 rare diseases and believe that approximately 80 percent have a genetic origin.

In 1989, the National Commission on Orphan Diseases considered the lack of specialized centers for the diagnosis and treatment of rare diseases to be a serious barrier to the advancement of research on rare diseases. The commission found that 15 percent of patients with rare diseases had to wait 5 years or more to obtain a correct diagnosis. An additional 30 percent of patients waited 1 to 5 years before obtaining a diagnosis.

In 1989, the National Commission on Orphan Diseases found that 15 percent of patients with rare diseases had to wait 5 years or more to obtain a correct diagnosis. An additional 30 percent of patients waited 1 to 5 years before obtaining a diagnosis.

In 1999, the NIH Special Emphasis Panel on the Coordination of Rare Diseases Research endorsed the need for specialized centers for rare diseases. The panel recommended funding for specialized research and diagnostic centers for major categories of rare diseases. The panel recommended establishing rare diseases centers of excellence on a graduated basis, starting with 10 regional centers in the first year with incremental increases of 10 centers per year until NIH had established 40 regional centers. The panel also emphasized that centers should work closely with patient advocacy groups. Congress realized the panel's recommendations with the Rare Diseases Act of 2002, Pub. L. No. 107-280. In response to the Act, NIH established the Rare Diseases Clinical Research Network (RDCRN) in 2003. ORDR partnered with 6 NIH ICs to fund 10 RDCRN consortia that focused on rare disease groups at multiple academic institutions and shared a central Data and Technology Coordinating Center (DTCC).

In February 2008, ORDR, in collaboration with several NIH ICs, released two RFAs to recompete the network and establish Phase II of the RDCRN—Rare Diseases Clinical Research Consortia (RDCRC) for the Rare Disease Clinical Research Network [U54] (RFA-OD-08-001) and Data Management and Coordinating Center (DMCC) for the Rare Diseases Clinical Research Network [U54] (RFA-OD-08-002). Existing as well as potentially new consortia and data coordinating centers were invited to apply.

ORDR and 7 NIH Institutes funded and provided administrative support to 19 consortia and the DMCC (see Table 4-5) in FY 2009. These Phase II RDCRN awards are for 5 years.

How the RDCRN Functions within the NIH Framework

In 2009, the RDCRN grew from 10 to 19 consortia, 4 of which were funded through the American Recovery and Reinvestment Act (ARRA).

Originally, in Phase I, ORDR partnered with six NIH Institutes (NCRR, NICHD, NINDS, NIAMS, NIDDK, and NHLBI) in administering and funding the network. For Phase II of the network, ORDR is partnering with seven Institutes: NICHD, NIAMS, NINDS, NHLBI, the NIAID, NIDDK, and NIDCR.

Each consortium develops clinical protocols for a set of related rare diseases and includes several participating institutions. The network incorporates uniform data and methodological standards across all the consortia and their component sites. The original RDCRN contained more than 70 sites across the United States and in other countries. The current network

includes approximately 165 sites in at least 29 states. Twenty sites are in other countries. The total number of sites is expected to further facilitate enrollment of and access for patients.

The current Rare Diseases Clinical Research Network includes approximately 165 sites in at least 29 states. Twenty sites are in other countries.

A steering committee guides the network. The steering committee consists of the principal investigator of each consortium, NIH representatives, and a patient advocacy representative nominated by the 57 collaborating patient advocacy groups. The patient advocacy groups associated with each consortium have formed a coordinating committee that is instrumental in participating in the development of informed consent statements, informational materials about diseases and treatments, protocols, recruitment strategies, and other important activities. Other network committees and working groups facilitate communication and collaboration across and within consortia to ensure research efficiency and excellence.

In general, the current network's infrastructure and functions build on lessons learned and uses those approaches that have proven to be most efficacious.

Description of Diseases and Conditions under Study in Phase II of the RDCRN

With establishment of Phase II of the RCDRN, network researchers are poised to study 92 rare diseases, including:

Urea cycle disorders (UCD): UCDs are a group of genetic disorders caused by a deficiency of one of the enzymes in the urea cycle, which is responsible for removing ammonia from the blood stream. Because many cases of UCD remain undiagnosed, infants born with the disorders may die without a definitive diagnosis.

Vasculitides: Vasculitides are a heterogeneous group of diseases resulting in severe inflammation of blood vessels. Arteries and veins of any size in any organ may be affected, leading to damage to organs caused by a loss of the blood supply, known as ischemia.

Genetic Disorders of Mucociliary Clearance: Genetic disorders of mucociliary clearance include disorders such as primary ciliary dyskinesia (PCD), variant cystic fibrosis (CF), and pseudohypoaldosteronism (PHA). They reflect genetic defects in airway host-defense and impaired clearance of mucus, and typically result in severe chronic infection of the airways.

*Dystonias:*The dystonias are a group of neurological disorders characterized by involuntary twisting movements and unnatural posturing. Focal dystonias affect only one body part. Some of the most common forms of focal dystonia are cervical dystonia, affecting the neck; blepharospasm, affecting the eyelids; spasmodic (or laryngeal) dysphonia, affecting the voice box; craniofacial dystonia, affecting the lower face; and limb dystonias, affecting the hand or arm or foot or leg.

Brain vascular malformations: Brain vascular malformations are characterized by veins and blood vessels in the brain that are structurally malformed and can cause drainage of an area of the brain, resulting in repeated and debilitating bleeding, seizures, and hemorrhaging as a result of the formation of blood clots. Brain vascular malformations are resource-intensive to manage effectively, and have high probability of serious neurological morbidity. Specific medical therapies for these diseases are lacking.

*Immune-Mediated Disorders Post Transplant of Donor Bone Marrow:*Hematopoietic stem cell transplantation is the infusion of stem cells from the bone marrow of a donor into a patient to treat tumors, disorders of the blood, immunodeficiency syndromes, congenital enzyme deficiencies, and autoimmune disorders. Persons who receive grafts from donors (known as allogeneic or allografts) are at a substantially greater risk for graft-versus-host disease and delayed immune system recovery than are persons who receive grafts harvested from one location on their body and transplanted

to another site (autografts). Recipients of allografts also have greater rates of graft rejection, cytomegalovirus infection, invasive fungal infection, and Epstein-Barr virus-associated post-transplant lymphoproliferative disease, in which the body has too many white blood cells, which can overactivate the immune system.

Nephrotic Syndromes or Nephrosis: Nephrotic syndromes and nephrosis cause damage to the kidney, resulting in leakage of large amounts of protein into the urine. The loss of so much protein in the kidney causes other conditions, which are often characterized by excess body fluid.

Primary Immune Deficiencies: Primary immune deficiencies, also called primary immune disorders, weaken the immune system, allowing repeated infections to occur more easily. Many people with primary immunodeficiency are born without some of the body's immune defenses, which leaves them more susceptible to infections. In some cases, the body fails to produce any or enough antibodies to fight infection. In other cases, the cellular defenses against infection fail to work properly.

Lysosomal Storage Diseases: Lysosomal storage diseases are a large group of diseases, each characterized by a specific lysosomal enzyme deficiency in a variety of tissues. Consortium investigators study 11 lysosomal storage diseases—mucopolysaccharidoses (MPS), Batten disease, Niemann-Pick disease type C, mucolipidosis type IV, late infantile neuronal ceroid lipofuscinosis, glycoproteinoses, Wolman disease, Pompe disease, bone disease in the MPS, and Fabry disease. These conditions involve severe central nervous system disease, which is difficult to treat. They are devastating to quality of life and can lead to dementia and death.

Autonomic Rare Diseases: The autonomic nervous system controls vital involuntary body functions, such as blood pressure; heart and breathing rates; body temperature; digestion; metabolism; the balance of water and electrolytes; the production of saliva, sweat, and tears; urination; defecation; and sexual response. Disorders of the autonomic nervous system can affect any body part and may be reversible or progressive.

Charcot Marie Tooth Disease (CMT): CMT is an inherited disease involving damage to the nervous system. Even patients with this progressive disease who come from the same family show a wide range of symptoms. For example, progressive muscle wasting leads to problems with walking, running, and balance. Later in the course of the disease, hand function may become affected. Loss of nerve function in the extremities also can result in sensory loss. People can be unaware of having developed ulcers of the feet or of cuts or burns on the hands. Sensory loss can lead to gradual hearing impairment and, sometimes, deafness. Some people with CMT also have tremors, usually of the hands. Weakness of the respiratory muscles can cause life-threatening problems. Scoliosis of the spine also is associated with this disease. No effective therapies are available for any form of CMT.

Hereditary Nephrolithiasis and Kidney Failure: Hereditary causes of nephrolithiasis and kidney failure are inborn errors of metabolism that lead to high concentrations of insoluble mineral salts in the urine and severe, recurrent kidney stones. Patients with primary hyperoxaluria (PH), cystinuria, adenine phosphoribosyltransferase deficiency (dihydroxyadeninuria [DMA]), and Dent disease experience stones beginning in childhood. All patients with hereditary nephrolithiasis and kidney failure experience deposition of crystals in kidney tissue and loss of kidney function. Disease expression varies widely. Some PH patients progress to end-stage renal failure during infancy. Progress toward effective treatment has been slow.

Porphyrias: Porphyrias are a group of inherited metabolic disorders that arise as a result of a malfunction in one of the eight steps in the body's synthesis of a complex molecule called "heme," which is essential for the transport of oxygen to cells in the body. A common feature of all porphyrias is the accumulation in the body of porphyrins, chemicals that are normally present in the body but do not normally accumulate, or porphyrin precursors. The type of porphyria depends on which of these chemicals builds up. Symptoms include effects on the nervous system and burning, blistering, and scarring of sun-exposed areas of the skin.

Angelman, Rett, and Prader-Willi Syndromes: Angelman syndrome is a complex genetic disorder that primarily affects the nervous system and causes developmental delay, intellectual disabilities, severe speech impairment, seizures, small head size, and problems with movement and balance in young children. Rett syndromeis a childhood neurodevelopmental disorder characterized by normal early development followed by loss of purposeful use of the hands, distinctive hand movements, slowed brain and head growth, gait abnormalities, seizures, and intellectual disabilities. Prader-Willi Syndrome (PWS) is a rare genetic disorder that causes poor muscle tone, low levels of sex hormones, and a constant feeling of hunger.

Sterol and Isoprenoid Disease: Sterol and isoprenoid diseases are a group of rare diseases bound by common biochemistry and severe impact on health: cerebrotendinous xanthomatosis (CTX), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), Niemann-Pick disease type C (NPC), sitosterolemia, Sjogren-Larsson syndrome (SLS), and Smith-Lemli-Opitz syndrome (SLOS).

Salivary Gland Carcinomas: Salivary gland carcinomas are comprised of widely varied subtypes with different clinical behaviors and can result in disfigurement, death, or both. In general, salivary gland carcinomas afflict individuals later in life. The cause of salivary gland tumors remains unknown. Of the risk factors investigated, exposure to radiation has been the only known factor associated with salivary gland tumors. Individual differences in sensitivity to radiation have been implicated as an underlying cause for the development of these tumors.

Inherited Spinocerebellar Ataxias: Inherited forms of spinocerebellar ataxias 1, 2, 3, and 6 are a heterogeneous group of disorders characterized by degenerative symptoms in the cerebellum, spinal cord, and brain stem. Ataxia means “loss of the ability to coordinate muscular movement.” Degenerative ataxias show continuous worsening of the disease, leading to severe disability or death. Currently, there are no treatments for these disorders.

Neurologic Channelopathies: Nervous system channelopathies include episodic ataxias, non-dystrophic myotonic disorders, and Andersen-Tawil syndrome. The episodic ataxias are characterized by attacks of clumsiness and imbalance triggered by factors such as stress or fatigue. Episodic ataxia type 1 is characterized by episodes of imbalance with fine twitching or rippling of muscles, which is difficult to see except in small muscles of the hands and face. Episodic ataxia type 2 is characterized by episodes of slurring of speech, gait imbalance, and dysfunction of eye movements. The non-dystrophic myotonias are a very rare group of muscle disorders caused by abnormalities in different muscle cell membrane proteins. Patients experience impaired muscle relaxation that causes impaired physical activity, pain, and weakness. There are no proven therapies, and it is not known if treatment should differ for different disease subtypes. Andersen-Tawil syndrome is a rare form of periodic paralysis that affects the function of skeletal and heart muscles. Periodic paralysis is characterized by episodes of muscle weakness.

Respiratory Chain Mitochondrial Diseases: Mitochondrial diseases due to defects of the respiratory chain are clinically and genetically diverse; occur most often in infants, children, and young adults; and can be fatal. (Mitochondria are units within cells that generate its energy. The “respiratory chain” is the process by which mitochondria generate potential energy). Diagnosis of respiratory chain mitochondrial disease is difficult because of the broad variability in symptoms. Many of these diseases progress rapidly, and no treatments currently exist. The common link that these diseases share is the inability of the mitochondria to completely burn food and oxygen, a critical function for the mitochondria to generate the energy needed by cells to function properly. Mitochondrial impairment results in a host of devastating conditions, including respiratory chain diseases with complex clinical features, such as neurological and muscular dysfunction often accompanied by kidney dysfunction, hormone, cardiac, and liver complications.

More information on these rare diseases is available in the NIH Rare Diseases and Related Terms glossary at http://rarediseases.info.nih.gov/RareDiseaseList.aspx?PageID=1.

Burden of Illness

The burden of illness for all rare diseases is difficult to assess because of the large number of disorders, the complexity of each disease, and the limited availability of prevalence and incidence data. The National Organization for Rare Disorders (NORD) estimates that 25-30 million people in the United States have a rare disease.

Overall, rare diseases are devastating and costly. This is due partly because of their severity and partly because diagnosis can take a long time, often occurring well after symptoms have appeared. In addition, often treatment is not available once a disease is diagnosed. Moreover, scientists cannot assess the pain, suffering, and lost opportunities experienced by patients and their families.

The National Organization for Rare Disorders estimates that 25-30 million people in the United States have a rare disease.

Scope of NIH Activities: Research and Programmatic

The RDCRN brings together experts who are skilled in studying, diagnosing, and treating particular groups of rare diseases and who are eager to train junior faculty and postgraduate fellows. In addition, the network enables each consortium to gather groups of patients with similar or related disorders, fosters basic scientific investigation and longitudinal natural history and epidemiological studies, encourages synergy in translational research, and enhances opportunities for collaborative clinical investigation. The 2003-2008 DTCC and the current DMCC enable sharing of study results nationally and internationally in a timely and uniform way. Although the DMCC has primary responsibility for the coordination and management of data, participating RDCRN institutions, NIH program officers, and patient advocacy group representatives provide input and participate actively in overall data coordination.

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the RDCRN in FY 2008 was $10.2 million for 10 consortia and the DTCC. In FY 2009, actual funding for the 19 consortia and the DMCC was $23.4 million, including $2.1 million from ARRA funds. The total cost over 5 years for the RDCRN's Phase II is estimated to be $117 million.

FY 2008 and FY 2009 Progress Report

Programmatic and Research Activities and Outcomes

Throughout its first funding cycle, the RDCRN cumulatively enrolled more than 5,500 patients in 37 clinical studies. Patient recruitment for clinical studies is a fundamental challenge in rare diseases research because typically there are few affected patients in any one geographic area. The RDCRN is designed to address this problem by fostering collaboration among scientists and sites and shared access to geographically distributed research resources.

Patient recruitment for clinical studies is a fundamental challenge in rare diseases research because typically there are few affected patients in any one geographic area. The RDCRN is designed to address this problem by fostering collaboration among scientists and sites and shared access to geographically distributed research resources.

The Coalition of Patient Advocacy Groups included representatives of 57 patient advocacy groups by late 2009. The coalition assists in many aspects of network research and publications. The protocols ranged from natural history studies to research on biomarkers, treatment efficacy, and genotype-phenotype correlations; genetic analyses; Phase I and II clinical trials; and pilot projects.

The Rare Diseases Clinical Research Network benefits from a coalition of patient advocacy groups that grew to 57 in 2009. The coalition assists in many aspects of network research and the development of educational materials.

The RDCRN is unique in its approach to addressing rare diseases as a group. Previously, the NIH ICs funded research on individual rare diseases in their respective disease-type or organ domain. The network established a comprehensive training program for clinical investigators and developed a network-wide website to inform the public, physicians, patients, and investigators about the rare diseases under study. The network's aims continue to include training a cadre of young investigators in the clinical, pathophysiologic (physiological process associated with disease), and pharmacologic aspects of specific rare diseases. The network's training includes instruction on and experience with methodologies for patient-oriented clinical research in rare diseases, including biostatistics and epidemiology; and the conceptualization, ethics, design, implementation, analysis, and reporting of controlled clinical trials. An integrated training program provides supervision by clinicians and biostatisticians with extensive experience in investigating rare diseases and developing novel therapies. The training program also provides an integrated statistics, epidemiology, and computer science curriculum; seminars on clinical trial design; courses in the basic sciences underlying experimental therapeutics and in ethics; career development support; participation and collaboration with network faculty with expertise in designing rare diseases studies; clinical experience in intensively investigating disease states; and mentoring to achieve an independent academic career in rare diseases.

The Data and Technology Coordinating Center created a central public website, developed as a portal for the rare diseases community, including patients and their families and health care professionals. The website provides information on rare diseases research, consortium activities, approved protocols, disease information, and practice guidelines. The website had more than 3.4 million visits in 2008.

The RDCRN is the first program that aims to create a specialized infrastructure to support rare diseases research. The DTCC developed and enabled new technologies, tools, and services for the network. These tools and services included electronic data entry, remote direct laboratory transfer, vocabulary and laboratory standards, statistical support, website development and maintenance, and database-querying tools. The DTCC, in collaboration with each consortium, also implemented an effective patient contact registry that allows individuals to register to receive information about new or ongoing clinical studies in addition to periodic educational updates and to consider participating in clinical studies. To facilitate patients' transportation to RDCRN sites, Angelflight NIH links patients with volunteer pilots who donate their time, planes, fuel, and operating expenses to transport patients and family members free of charge. By accepting donated frequent flyer miles, Angelflight also provides free tickets from select commercial airlines. The goal of the program is to ensure that no patient is denied access to medical evaluation or ongoing research projects because of a lack of air transportation.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the RDCRN

In 2008, ORDR and participating NIH program staff reviewed the RDCRN's progress before publishing two RFAs. As a result of this review, ORDR staff decided to open the RFAs to the incumbent consortia and the DTCC as well as to new applicants. Some consortia were not renewed and many new consortia were added to the network.

ORDR and NCRR convened a workshop on July 16, 2009, titled "Advancing Rare Diseases Research through Networks and Collaboration." The workshop featured several speakers from the RDCRN and addressed the advantages and occasional disadvantages of multicenter collaborations in rare diseases research, trainee experiences, patient recruitment, outreach and dissemination, strategies for forming effective teams and networks, the interplay of basic and clinical research in the translation process, and the application of clinical research findings to clinical practice. Suggestions for improvements from workshop speakers included further increasing the number of sites in each consortium, even if this increase could result in fewer participants per site, and including more biostatisticians with expertise in small patient

populations early in protocol development at participating institutions in addition to central technical support from the DMCC.

Evaluation Plans

Because the RDCRN has been in operation only since 2003, it has not yet been formally evaluated to assess the impact of its research and training activities. Until that is possible, NIH will continue to regularly review RDCRN performance via scrutiny of progress reports, site visits, and program reviews.

When the RDCRN's impact on research and its contribution to rare diseases treatment is more mature and measurable, the RDCRN's contribution to the health of the Nation will be determined using the following criteria:

- Study completion and outcomes
- Timely recruitment of adequate patient populations
- Number of trainees who complete their training programs
- Trainees' impact on the rare disease field
- Impact of scientific publications on future rare diseases research

Contribution of the DTCC and subsequent DMCC to research in the form of a coordinated data management system; the ability to capture and integrate many different types of data; and the development and broad acceptance of novel technological approaches to distributed computing, federated databases, and data mining within and across diseases.

Future Directions

ORDR and its partner Institutes will continue to work with the RDCRN and encourage the continued training of new rare diseases researchers. The current consortia and the DMCC will build on the experience and lessons learned in the program's previous years. ORDR hopes that in response to the recommendations of the 1999 NIH Special Emphasis Panel on the Coordination of Rare Diseases Research, the numbers of consortia, sites in each consortium, trainees, and patients served will continue to increase in the United States and in other countries. As a result, patients and their families will be able to look forward to better treatments and cures, improving the duration and quality of their lives.

Table 4-5. Rare Diseases Clinical Research Network

Institution and Location	Year Established
Boston University School of Medicine, Boston, MA	2003
Children's National Medical Center, Children's Research Institute, UCDC, Washington DC	2003
University of Alabama at Birmingham, AL (previously Baylor College of Medicine, Houston, TX)	2003
University of Rochester, NY	2003
University of South Florida, Tampa, FL (DMCC)	2003
University of North Carolina, Chapel Hill, NC	2004
Columbia University Medical Center, New York, NY	2009
Emory University, Atlanta, GA	2009
Fred Hutchinson Cancer Research Center, Seattle, WA	2009

Institution and Location	Year Established
Mayo Clinic College of Medicine, Rochester, MN	2009
Mount Sinai School of Medicine of NYU, New York, NY	2009
Oregon Health and Sciences University, Portland, OR	2009
University of California, San Francisco, CA	2009
University of Florida, Gainesville, FL	2009
University of Michigan at Ann Arbor, MI	2009
University of Minnesota Twin Cities, Minneapolis-St. Paul, MN	2009
University of Texas MD Anderson Cancer Center, Houston, TX	2009
Vanderbilt University Medical Center, Nashville, TN	2009
Wayne State University, Detroit, MI	2009

Autism Centers of Excellence

Overview

Why the Autism Centers of Excellence Were Established

Recent studies suggest that autism spectrum disorders (ASD) affect approximately 1 in 110 children in the United States.[48] Because of the urgent need to better understand the causes of ASD and develop treatments for these serious and disabling disorders, Congress passed the Combating Autism Act of 2006. This Act emphasized the need to expand research and improve coordination among NIH Centers of Excellence focused on ASD. The new Autism Centers of Excellence (ACE) program, the funding of which began in FY 2007 and FY 2008, focuses on identifying the causes of ASD and developing new and improved treatments.

In response to the Combating Autism Act, the NIH Autism Coordinating Committee (ACC) formed the ACE program by consolidating the aims of two previous ASD research programs into a single research effort (see Table 4-6). The previous programs were the Collaborative Programs of Excellence in Autism (CPEA, established in 1997) and Studies to Advance Autism Research and Treatment (STAART, established in 2002 and completed in 2008). This report will focus mainly on the goals, activities, and accomplishments of the ACE program. The ACC itself also was formed at the request of Congress and comprises representatives from five ICs.

How the Autism Centers of Excellence Function within the NIH Framework

The Children's Health Act of 2000 established the Interagency Autism Coordinating Committee (IACC), which includes Federal agency representatives and members of the public appointed by the Secretary of HHS. At the request of Congress, the IACC developed an Autism Research Matrix. The matrix delineated goals and action items in epidemiology, the characterization of ASD, the role of the environment, neuroscience, screening, early intervention, specific treatments, and school and community interventions, to guide NIH-funded ASD research. ACE grantees are addressing the matrix goals, particularly the goals of identifying the causes of ASD and developing treatments.

The NIH ACC established the goals of the ACE program, and the NIH ICs share administrative and oversight responsibilities. The ACE program comprises centers and a network infrastructure. ACE centers foster multidisciplinary collaboration among teams of specialists at a single facility to address a particular research problem in depth. Each center conducts interdependent sub-projects. ACE networks unite researchers at many different facilities throughout the country; working as a unit, each network addresses a single research question. Because networks encompass multiple sites, they can recruit large numbers of participants with ASD, achieving optimal design for treatment trials. A program officer and grants management officer at the awarding NIH Institute administer each ACE award.

The Combating Autism Act of 2006 expanded the scope of the IACC. In accordance with the new law, the IACC develops and updates annually a strategic plan for ASD research and a summary of ASD research advances. The IACC also monitors and makes recommendations about Federal ASD-related activities. The priorities and progress of the ACE program will be an integral component of these annual activities.

In January 2009, the Interagency Autism Coordinating Committee released the first edition of its Strategic Plan for Autism Spectrum Disorder Research. Consistent with the Strategic Plan, the six ACE centers and five networks that comprise the ACE program have begun research on biomarkers, genetic susceptibility to ASD, pharmacological treatments, early intervention, and risk and protective factors for ASD.

In January 2009, the IACC released the first edition of its Strategic Plan for Autism Spectrum Disorder Research. The Strategic Plan advises Federal agencies and Congress on needs and opportunities in ASD research. The scientific

community, service providers, advocates, parents, and people with ASD contributed to the Plan. The Plan has six sections focused on six critical questions asked by people and families living with ASD:

- When should I be concerned?
- How can I understand what is happening?
- What caused this to happen and can this be prevented?
- Which treatments and interventions will help?
- Where can I turn for services?
- What does the future hold?

The NIH ACC plays an integral role in coordinating NIH activities inspired by and relevant to the Strategic Plan. Consistent with the Strategic Plan, the six ACE centers and five networks that comprise the ACE program have begun research on biomarkers, genetic susceptibility to ASD, pharmacological treatments, early intervention, and risk and protective factors for ASD.

Description of Disease or Condition

Leo Kanner first described autism in 1943 as a disorder "characterized by extreme aloneness and a desire for the preservation of sameness, with a variety of behavioral (cognitive, affective) symptoms derived from them."[49] Over time, growing recognition of a broader range of related disorders led to the use of the term autism spectrum disorders (ASD), which includes several complex neurodevelopmental disorders of early childhood that vary in severity, share common clinical features, and persist throughout the lifetime of the individual. Common features include social impairments; verbal and nonverbal communication difficulties; and restricted, repetitive, and stereotyped behavior patterns. "Classic" autistic disorder is the most disabling; other forms of ASD, such as Asperger's disorder, have fewer or milder symptoms. Intellectual disabilities, seizures, and self-abusive behaviors are common among children at the more severe end of the spectrum.

A child's primary caregivers often are the first to identify ASD symptoms. As early as infancy, a baby with ASD may be unresponsive to people or focus intently on one item to the exclusion of others for long periods. A child with ASD may appear to develop normally and then withdraw and become indifferent to social engagement. Clinicians can make a reliable ASD diagnosis for most children by age 3. The current ASD diagnostic criteria and classifications represent progress in identifying a core set of developmental symptoms that, in the past, clinicians might have diagnosed differently because the criteria were more narrowly defined than they are today.

Burden of Illness

ASD causes tremendous economic and social burdens for families and society at large. Although ASD varies greatly in character and severity, it occurs in all ethnic and socioeconomic groups and affects every age group. Currently, no coherent and comprehensive system of care is available for affected individuals. People with ASD might receive private and public services in special education settings, hospitals, university medical centers, or residential treatment facilities, among others.

Some scientists and economists have estimated that the combined direct and indirect costs of providing care for all Americans with ASD during their lifetimes exceed $34 billion. The estimated costs over a lifetime for each person total $3 million.

Some scientists and economists have estimated that the combined direct and indirect costs of providing care for all Americans with ASD during their lifetimes exceed $34 billion. The estimated costs over a lifetime for each person total $3 million.[50] Families often incur large debts for medical and education services that public programs or medical insurance do not cover. In addition, autism often leads to profound emotional hardships for patients and their families.

CDC currently estimates that as many as 9.0 per 1,000 children have an ASD.[51] The total number of individuals in the United States with an ASD diagnosis is unknown. However, CDC estimates that up to 730,000 individuals age 21 or younger have an ASD (assuming a prevalence rate of 1 in 110, a birth rate of 4 million children per year in the United States, and a constant prevalence rate over the past 20 years). Boys are approximately four times as likely as girls are to have an ASD.[52]

Prevalence estimates, or the number of affected individuals at a given point in time, have increased markedly since the early 1990s. However, it is unclear if incidence, the number of new cases across time in the same population, also has increased. It also is unclear whether the rise in prevalence is due to such factors as the use of different criteria to diagnose ASD or earlier and more accurate ASD diagnoses. A similar increase in ASD prevalence has occurred in other countries.

Scope of NIH Activities: Research and Programmatic

The six centers and five networks that compose the ACE program cover a broad range of ASD research areas, including early brain development and functioning, social interactions in infants, rare genetic variants and mutations, associations between autism-related genes and physical traits, possible environmental risk factors and biomarkers, and a potential new treatment.

In the past, ASD researchers collected clinical data using different formats and analysis methods and stored data in different locations. This approach made comparing data from different sites difficult. ASD researchers now can use the National Database for Autism Research to gather and analyze data.

In the past, ASD researchers collected clinical data using different formats and analysis methods and stored data in different locations. This approach made comparing data from different sites difficult. ASD researchers now can use the National Database for Autism Research (NDAR), a common bioinformatics system, to gather and analyze data from human subjects. The NDAR has built on the collaborative aspects of the STAART data coordinating center and makes gathering, evaluating, and sharing ASD research data from a variety of sources easier and faster for researchers. NDAR allows the seamless integration of data, research tools, and research projects from institutions across the United States and internationally.

All ACE centers and networks are contributing data to NDAR. In addition, efforts to add data from the STAART data coordinating center are underway. NDAR also will coordinate data access with other Federal databases, such as the NIMH Center for Collaborative Genetic Studies. The center is a national resource for researchers who study the genetics of complex mental disorders, including ASD, and stores human DNA, cell cultures, and clinical data.

NIH Funding for FY 2008 and FY 2009

Three NIH ICs fund the ACE program—NICHD, NINDS, and NIMH. Actual NIH funding for the ACE program, which includes centers (P50s), a cooperative agreement (U01), and networks (R01s), was $25.2 million in FY 2008 and $26.5 million in FY 2009, including $1.89 million from ARRA funds.

FY 2008 and FY 2009 Progress Report

Programmatic and Research Activities and Outcomes

Several accomplishments of the ACE program and one of the STAART centers (funded through 2008) are highlighted briefly below.

- Researchers at **Yale University** are searching for biomarkers of visual engagement and auditory perception in infants at risk for ASD.

- Researchers at the **University of Illinois at Chicago** are studying genetic factors as well as brain chemicals and brain functions that could account for repetitive behaviors in people with ASD. They also are testing whether genetic differences influence how individuals respond to certain medications intended to reduce the frequency of these behaviors.
- Researchers at the **University of Washington** are investigating genetic and other factors that might increase a person's risk of having an ASD and factors that might protect people from getting an ASD.
- Investigators involved in the **University of North Carolina at Chapel Hill** ACE network are studying abnormal processes in early brain development by examining brain images of very young children at risk for developing ASD.
- The **University of California, San Diego,** ACE is using brain imaging methods to track brain development in children believed to be at risk for ASD. The researchers aim to identify brain or other physical differences that might increase a child's risk of developing ASD.
- Researchers at the **University of California, Los Angeles,** are determining the causes and treatments of social communication problems in people with ASD.
- The **University of Pittsburgh** ACE is studying how people with ASD learn and understand information.
- Researchers at the **Drexel University** network sites are studying possible risk factors and biological indicators of ASD before and soon after birth. This project is part of the Early Autism Risk Longitudinal Investigation (EARLI).

Researchers at the Drexel University network sites are studying possible risk factors and biological indicators of ASD before and soon after birth. This project is part of the Early Autism Risk Longitudinal Investigation (EARLI).

- Researchers at the **University of California, Davis,** network sites are examining factors that might be useful for improving treatment outcomes in very young children with autism. They are comparing an intensive behavioral intervention to standard community-based treatment.
- Investigators at **Wayne State University** network sites will conduct a clinical trial to test the safety and efficacy of buspirone, a drug that increases the body's production of serotonin—one of several neurotransmitters that brain cells use to communicate with each other—as an early intervention in children younger than 6 years with ASD. A pilot study by the Wayne State researchers showed that buspirone improves social interaction and reduces repetitive behaviors, sensory dysfunction (extreme sensitivity or lack of sensitivity to light, noise, and touch), and anxiety in children with autism.

Investigators at Wayne State University network sites will conduct a clinical trial to test the safety and efficacy of buspirone, a drug that increases the body's production of serotonin—one of several neurotransmitters that brain cells use to communicate with each other—as an early intervention in children younger than 6 years with ASD.

- Researchers at the **University of California, Los Angeles,** network sites are studying the relationship between genes related to autism and physical features. They also are investigating rare genetic variations, mutations, and abnormalities that affect a person's risk for autism.
- In three separate studies of genetic risk factors linked to ASD, **STAART investigators, ACE investigators, and other collaborators** identified common and rare genetic factors that affect ASD risk. The results point to genes that are involved in forming and maintaining the connections between brain cells. These results confirm previous findings on the role of genes in ASD and abnormal brain wiring in people with ASD. The study findings are a significant step forward in a larger effort to understand the complex genetic architecture of ASD. The investigators recently published their findings in the journals *Nature*[53, 54] and *Annals of Human Genetics*.[55]
- **STAART investigators** collaborated in a multisite study to evaluate the efficacy of a drug, citalopram, to treat ASD symptoms. Citalopram selectively can inhibit the activity of serotonin, which might play a role in the repetitive behaviors associated with autism. The researchers recently published their results in the *Archives of General Psychiatry*.[56] After 12 weeks of treatment, roughly one out of three children in both the group that took citalopram and the group that took a placebo (medicine with no active ingredients) had fewer or less severe repetitive symptoms. However, the children in the citalopram group experienced more adverse side effects than the children in the placebo group. According to the researchers, the study results show that the drug is no better than placebo in treating ASD symptoms.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the Autism Centers of Excellence

Evaluation Plans

The Combating Autism Act of 2006 and the NIH Reform Act of 2006 require NIH to evaluate the performance and research outcomes of the ACE program. In 2008, NIH established a trans-NIH evaluation team to conduct the first evaluation, which will gather baseline, descriptive data on the implementation of the program. The evaluation will use a two-part approach, focusing on process evaluation questions related to program implementation and determining the feasibility of future evaluation efforts to assess the outcomes of the ACE program.

In 2010, HHS will provide Congress with a progress report on activities related to ASD that will include results from the initial ACE program evaluation. The report also will discuss the incidence of ASD, average age at diagnosis, average age of intervention start, effectiveness and outcomes of interventions by subtype, and effectiveness and outcomes of newly developed intervention strategies.

Future Directions

In 2010, the NIH ACC plans to convene a 2-day meeting at which the investigators will present the goals of their ACE and exchange ideas for collaborations. Some sessions will address data sharing options through the NDAR, with time allotted for a question-and-answer period with NDAR staff. ACE principal investigators and project principal investigators, as well as core directors and data managers, will be invited to attend. Principal investigators will be encouraged to invite K award (career development grant) recipients, fellows, and postdoctoral students from their laboratories. Approximately 55 to 65 ACE investigators are expected to attend this meeting, which will take place annually thereafter.

Table 4-6. Studies to Advance Autism Research and Treatment (STAART) Centers

Institution and Location	Year Established
University of North Carolina, Chapel Hill, NC	2002
Yale University, New Haven, CT	2002
Boston University, Boston, MA	2003
Kennedy Krieger Institute, Baltimore, MD	2003
Mt. Sinai Medical School, New York, NY	2003
University of California, Los Angeles, CA	2003
University of Rochester, Rochester, NY	2003
University of Washington, Seattle, WA	2003

Table 4-7. Autism Centers of Excellence (ACEs)

Institution and Location	Year Established
University of California, Davis, CA	2007
University of California, Los Angeles, CA	2007
University of California, San Diego, CA	2007
University of Illinois, Chicago, IL	2007
University of North Carolina, Chapel Hill, NC	2007
University of Pittsburgh, Pittsburgh, PA	2007
University of Washington, Seattle, WA	2007
Yale University, New Haven, CT	2008
Wayne State University, Detroit, MI	2008
University of California, Los Angeles, CA	2008
Drexel University, Philadelphia, PA	2008

[48] Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators, Centers for Disease Control and Prevention (CDC). *MMWR Surveill Summ* 2009;58:1-20. PMID: 20023608.
[49] Kanner L. *Nerv Child* 1943;2:217-50.
[50] Ganz ML. *Arch Pediatr AdolescMed* 2007;161:343-9. PMID: 17404130.
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[53] Wang K, et al. *Nature* 2009;459:528-33. PMID: 19404256.
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[55] Ma D, et al. *Ann Hum Genet* 2009;73(Pt 3):263-73. PMID: 19456320.
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5 APPENDICES

Biennial Report of the Director

National Institutes of Health

Fiscal Years 2008 & 2009

Volume V

NIH Publication No. 11-7701
U.S. Department of Health and Human Services
National Institutes of Health

An electronic version of this report is available at: http://biennialreport.nih.gov and contains many live links to NIH programs, plans, and publications.

Volume V Contents

Contents of Other Volumes

Appendix A: Legal Mandates for this Report

Pub. L. No. 109-482: The National Institutes of Health Reform Act of 2006 (Relevant Provisions)

An Act

To amend title IV of the Public Health Service Act to revise and extend the authorities of the National Institutes of Health, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "National Institutes of Health Reform Act of 2006".

TITLE I—NIH REFORM

- -

SEC. 102. AUTHORITY OF DIRECTOR OF NIH.

- -

(b) ADDITIONAL AUTHORITIES.—Section 402(b) of the Public Health Service Act, as amended by subsection (a) of this section, is amended by striking paragraphs (2) and (3) and inserting the following:

- -

"(7)(A) shall, through the Division of Program Coordination, Planning, and Strategic Initiatives—

" (i) identify research that represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that deserve special emphasis and would benefit from conducting or supporting additional research that involves collaboration between 2 or more national research institutes or national centers, or would otherwise benefit from strategic coordination and planning;

"(ii) include information on such research in reports under section 403;

- -

SEC. 104. REPORTS

(a) REPORT OF DIRECTOR OF NIH.—The Public Health Service Act (42 U.S.C. 201 et seq.), as amended by section 103(a) of this Act, is amended—

- -

(3) by striking section 403 and inserting the following sections:

"SEC. 403. BIENNIAL REPORTS OF DIRECTOR OF NIH.

"(a) IN GENERAL.—The Director of NIH shall submit to the Congress on a biennial basis a report in accordance with this section. The first report shall be submitted not later than 1 year after the date of the enactment of the National Institutes of Health Reform Act of 2006. Each such report shall include the following information:

"(1) An assessment of the state of biomedical and behavioral research.

"(2) A description of the activities conducted or supported by the agencies of the National Institutes of Health and policies respecting the programs of such agencies.

"(3) Classification and justification for the priorities established by the agencies, including a strategic plan and recommendations for future research initiatives to be carried out under section 402(b)(7) through the Division of Program Coordination, Planning, and Strategic Initiatives.

"(4) A catalog of all the research activities of the agencies, prepared in accordance with the following:

"(A) The catalog shall, for each such activity—

"(i) identify the agency or agencies involved;

"(ii) state whether the activity was carried out directly by the agencies or was supported by the agencies and describe to what extent the agency was involved; and

"(iii) identify whether the activity was carried out through a center of excellence.

"(B) In the case of clinical research, the catalog shall, as appropriate, identify study populations by demographic variables and other variables that contribute to research on minority health and health disparities.

"(C) Research activities listed in the catalog shall include, where applicable, the following:

"(i) Epidemiological studies and longitudinal studies.

"(ii) Disease registries, information clearinghouses, and other data systems.

"(iii) Public education and information campaigns.

"(iv) Training activities, including—

"(I) National Research Service Awards and Clinical Transformation Science Awards;

"(II) graduate medical education programs, including information on the number and type of graduate degrees awarded during the period in which the programs received funding under this title;

"(III) investigator-initiated awards for postdoctoral training;

"(IV) a breakdown by demographic variables and other appropriate categories; and

"(V) an evaluation and comparison of outcomes and effectiveness of various training programs.

"(v) Clinical trials, including a breakdown of participation by study populations and demographic variables and such other information as may be necessary to demonstrate compliance with section 492B (regarding inclusion of women and minorities in clinical research).

"(vi) Translational research activities with other agencies of the Public Health Service.

"(5) A summary of the research activities throughout the agencies, which summary shall be organized by the following categories, where applicable:

"(A) Cancer.

"(B) Neurosciences.

"(C) Life stages, human development, and rehabilitation.

"(D) Organ systems.

"(E) Autoimmune diseases.

“(F) Genomics.

“(G) Molecular biology and basic science.

“(H) Technology development.

“(I) Chronic diseases, including pain and palliative care.

“(J) Infectious diseases and bioterrorism.

“(K) Minority health and health disparities.

“(L) Such additional categories as the Director determines to be appropriate.

“(6) A review of each entity receiving funding under this title in its capacity as a center of excellence (in this paragraph referred to as a `center of excellence'), including the following:

“(A) An evaluation of the performance and research outcomes of each center of excellence.

“(B) Recommendations for promoting coordination of information among the centers of excellence.

“(C) Recommendations for improving the effectiveness, efficiency, and outcomes of the centers of excellence.

“(D) If no additional centers of excellence have been funded under this title since the previous report under this section, an explanation of the reasons for not funding any additional centers.

“(b) Requirement Regarding Disease-Specific Research Activities.— In a report under subsection (a), the Director of NIH, when reporting on research activities relating to a specific disease, disorder, or other adverse health condition, shall—

“(1) present information in a standardized format;

“(2) identify the actual dollar amounts obligated for such activities; and

“(3) include a plan for research on the specific disease, disorder, or other adverse health condition, including a statement of objectives regarding the research, the means for achieving the objectives, a date by which the objectives are expected to be achieved, and justifications for revisions to the plan.

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SEC. 106. ENHANCING THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD.

(a) IN GENERAL.—In administering the Clinical and Translational Science Award, the Director of NIH shall establish a mechanism to preserve independent funding and infrastructure for pediatric clinical research centers by—

- -

(b) REPORT.—As part of the biennial report under section 403 of the Public Health Service Act, the Director of NIH shall provide an evaluation and comparison of outcomes and effectiveness of training programs under subsection (a).

Public Law 110-85: The Food and Drug Administration Act of 2007 (Relevant Provisions)

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the post market authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Food and Drug Administration Amendments Act of 2007."

- -

TITLE XI—OTHER PROVISIONS

Subtitle A—In General

- -

SEC. 1104. NIH TECHNICAL AMENDMENTS.

The Public Health Service Act (42 U.S.C. 201 et seq.) is amended—

- -

(3) in section 403(a)(4)(C)(iv)(III), by inserting "and postdoctoral training funded through research grants" before the semicolon;

Public Law 110-204: The Newborn Screening Saves Lives Act of 2007 (Relevant Provisions)

An Act

To amend the Public Health Service Act to establish grant programs to provide for education and outreach on newborn screening and coordinated follow-up care once newborn screening has been conducted, to reauthorize programs under part A of title XI of such Act, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This act may be cited as the "Newborn Screening Saves Lives Act of 2007".

- -

SECTION 7. CONTINGENCY PLANNING.

Part A of title XI of the Public Health Service Act (42 U.S.C. 300b-1 et seq.) as amended by section 6, is further amended by adding at the end the following:

- -

"SEC. 1116. HUNTER KELLY RESEARCH PROGRAM.

(a) NEWBORN SCREENING ACTIVITIES. —

"(1) IN GENERAL. —The Secretary , in conjunction with the Director of the National Institutes of Health and taking into consideration the recommendations of the Advisory Committee, may continue carrying out, coordinating, and expanding research in newborn screening (to be known as 'Hunter Kelly Newborn Screening Research Program') including —

- -

"(c) REPORTS .—The Director is encouraged to include information about the activities carried out under this section in the biennial report required under section 403 of the National Institutes of Health Reform Act of 2006.

Appendix B: Priorities and Plans of the Institutes and Centers and the Program Offices in the Office of the Director

This appendix provides brief descriptions of the missions of the NIH Institutes and Centers (ICs) and the program offices in the Office of the Director. Links to strategic plans (or strategic planning Web sites) are embedded in the names of the ICs and offices. The ICs are presented in the order in which they appear on the appropriation table in the Congressional Justification. The mission statements and strategic plans presented here classify and justify NIH priorities.

NIH Institutes and Centers

National Cancer Institute (NCI). NCI leads a national effort to reduce the burden of cancer. The National Cancer Act of 1971 broadened the scope and responsibilities of NCI and created the National Cancer Program, which conducts and supports basic and clinical biomedical research; training; health information dissemination; and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer and HIV/AIDS; rehabilitation from cancer; and the continuing care of cancer patients and their families. NCI aims for a future in which we can prevent cancer before it starts, identify cancers that do develop at the earliest stage, eliminate cancers through innovative treatment interventions, and biologically control those cancers that we cannot eliminate so they become manageable, chronic diseases.

National Heart, Lung, and Blood Institute (NHLBI). NHLBI provides leadership for a national research program in ddiseases of the heart, blood vessels, lung, and blood; sleep disorders; and blood resources management. The Institute plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigations and trials, observational studies, and demonstration and education projects. In addition, NHLBI plans and directs research in the development and evaluation of interventions and devices related to the prevention of diseases and disorders within its purview and the treatment and rehabilitation of patients who suffer from them. Also, the NHLBI oversees management of the NIH Women's Health Initiative.

National Institute of Dental and Craniofacial Research (NIDCR). NIDCR's mission is to improve oral, dental, and craniofacial health through research, research training, and the dissemination of health information. The Institute accomplishes its mission through basic and clinical research; training and career development programs that ensure an adequate number of talented, well-prepared, and diverse investigators; coordination across all sectors of the research community; and the timely transfer of knowledge gained from research and its implications for health to the public, health professionals, researchers, and policymakers.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). NIDDK conducts and supports basic and applied research and provides leadership for national programs in diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Several of these diseases are among the leading causes of disability and death and all can seriously affect the quality of life of those who have them.

National Institute of Neurological Disorders and Stroke (NINDS). NINDS aims to reduce the burden of neurological diseases and disorders. To accomplish this goal, the Institute conducts and supports basic, translational, and clinical research on the normal and diseased nervous system, fosters the training of investigators in the neurosciences, and seeks to better understand, diagnose, treat, and prevent neurological disorders. The NINDS research portfolio encompasses hundreds of neurological disorders, from diseases such as stroke that affect millions of people and are among the leading causes of death and disability, to rare disorders that individually affect a few people but collectively have an enormous impact on patients and families.

National Institute of Allergy and Infectious Diseases (NIAID). NIAID's mission is to conduct and support research to understand, treat, and prevent infectious and immune-related diseases. Infectious diseases include well-known killers such as HIV/AIDS, tuberculosis, and malaria; emerging or reemerging threats such as influenza and extensively drug-resistant tuberculosis (XDR-TB); and "deliberately emerging" threats from potential agents of bioterrorism. Immune-related disorders include autoimmune diseases such as rheumatoid arthritis as well as asthma, allergies, and problems associated with transplantation.

National Institute of General Medical Sciences (NIGMS). NIGMS supports basic biomedical research that increases the understanding of life processes and lays the foundation for advances in disease diagnosis, treatment, and prevention. The Institute's programs encompass the areas of cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, bioinformatics, computational biology, and minority biomedical research and training.

National Institute of Child Health and Human Development (NICHD). NICHD conducts and supports research on all stages of human development, from preconception to adulthood, to better understand the health of children, adults, families, and communities. This includes research on fertility, pregnancy, growth, developmental disabilities, and medical rehabilitation.

National Eye Institute (NEI). NEI conducts and supports research that helps prevent and treat eye diseases and other disorders of vision. This research leads to sight-saving treatments, reduces visual impairment and blindness, and improves the quality of life for people of all ages. NEI-supported research has advanced our knowledge of how the eye functions in health and disease.

National Institute of Environmental Health Sciences (NIEHS). The mission of NIEHS is to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease.

National Institute on Aging (NIA). NIA leads a broad scientific effort to understand the nature of aging and to extend the healthy, active years of life. The Institute provides leadership in aging research, training, health information dissemination, and other programs relevant to aging and older people and serves as the primary Federal agency on Alzheimer's disease research.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). NIAMS supports research to address the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; the training of basic and clinical scientists to carry out this research; and the dissemination of information on research progress in these diseases.

National Institute on Deafness and Other Communication Disorders (NIDCD). NIDCD conducts and supports biomedical research and research training on normal mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. In addition, NIDCD conducts and supports research and research training related to disease prevention and health promotion; addresses special biomedical and behavioral problems associated with persons who have communication impairments or disorders; and supports efforts to create devices that substitute for lost and impaired sensory and communication function.

National Institute of Mental Health (NIMH). The mission of NIMH is to transform the understanding and treatment of mental illness through basic and clinical research, paving the way for prevention, recovery, and cure. NIMH supports research and research training to fulfill the following four objectives: (1) Promote discovery in the brain and behavioral sciences to fuel research on the causes of mental disorders; (2) Chart mental illness trajectories to determine when, where, and how to intervene; (3) Develop new and better interventions that incorporate the diverse needs and circumstances of people with mental illness; and (4) Strengthen the public health impact of NIMH-supported research.

National Institute on Drug Abuse (NIDA). NIDA's mission is to lead the Nation in bringing the power of science to bear on drug abuse and addiction. This charge has two critical components. The first is the strategic support and conduct of research across a broad range of disciplines. The second is ensuring the rapid and effective dissemination and use of the results of that research to significantly improve prevention and treatment, and to inform policy as it relates to drug abuse and addiction.

National Institute on Alcohol Abuse and Alcoholism (NIAAA). NIAAA supports and conducts research focused on improving the treatment and prevention of alcoholism and alcohol-related problems to reduce the enormous health, social, and economic consequences of this disease. NIAAA conducts and supports research in a wide range of scientific areas including genetics, neuroscience, epidemiology, health risks and benefits of alcohol consumption, prevention, and treatment; coordinates and collaborates with international, national, State, and local institutions, organizations, agencies, and programs engaged in alcohol-related work; and communicates research findings to health care providers, researchers, policymakers, and the public.

National Institute of Nursing Research (NINR). NINR supports clinical and basic research to build the scientific foundation for clinical practice, prevent disease and disability, manage and eliminate symptoms caused by illness, enhance end-of-life and palliative care, and develop the next generation of scientists. The Institute’s scientific focus spans multiple disciplines and unites the biological and behavioral sciences to better understand the complex interactions between the physiological factors of health and disease and an individual’s knowledge, beliefs, and behavior.

National Human Genome Research Institute (NHGRI). NHGRI's mission has expanded since the initiation of the International Human Genome Project to encompass a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease. A critical part of the NHGRI mission continues to be the study of the ethical, legal, and social implications of genome research. NHGRI also supports the training of investigators and the dissemination of genome-related information to the public and health professionals.

National Institute of Biomedical Imaging and Bioengineering (NIBIB). NIBIB's mission is to improve health by leading the development and accelerating the application of biomedical technologies. The Institute is committed to integrating the physical and engineering sciences with the life sciences to advance research and medical care.

National Center for Research Resources (NCRR). NCRR provides laboratory scientists and clinical researchers with the environments and tools needed to make biomedical discoveries, translate these findings to animal-based studies, and then apply them to patient-oriented research. NCRR connects researchers with one another and with patients and communities across the Nation. These connections bring together innovative research teams and the power of shared resources, multiplying the opportunities to improve human health. Together, NCRR's four integrated and complementary divisions biomedical technology, clinical and translational research, comparative medicine, and research infrastructure accelerate and enhance research along the entire continuum of biomedical science.

National Center for Complementary and Alternative Medicine (NCCAM). NCCAM is dedicated to exploring complementary and alternative healing practices in the context of rigorous science; training complementary and alternative medicine researchers; and disseminating authoritative information to the public and professionals. To fulfill its mission, NCCAM supports a broad-based portfolio of research, research training, and educational grants and contracts, as well as various outreach mechanisms to disseminate information.

National Center on Minority Health and Health Disparities (NCMHD).[1] NCMHD promotes minority health and leads, coordinates, supports, and assesses NIH efforts to reduce and ultimately eliminate health disparities. In this effort, NCMHD supports and partners with other ICs to support basic, clinical, social, and behavioral research; promote research

infrastructure and training; foster emerging programs; disseminate health information; and reach out to minority and other communities that suffer from disparities in health.

John E. Fogarty International Center (FIC). FIC strengthens human and institutional capacity to confront complex global health challenges through innovative and collaborative research and training programs. It builds the knowledge and skills of developing country foreign scientists, identifies crucial gaps in global health research, and supports and advances the NIH mission through international partnerships.

National Library of Medicine (NLM). NLM is the world's largest research library of the health sciences, serving scientists, health professionals, and the public by collecting, organizing, and providing access to biomedical information. NLM also carries out programs designed to strengthen existing and develop new medical library services in the United States. It conducts research in health communications, supports medical informatics, and provides information services and sophisticated tools in the areas of molecular biology and toxicology/environmental health. NLM creates Web-based services for the general public containing information from NIH and other reliable sources. (Also see "The National Library of Medicine" in the section on "Capitalizing on Discovery," in Chapter 1.)

NIH Clinical Center. The Clinical Center is the NIH facility that provides the patient care, medical services, and environment necessary for NIH scientists to conduct clinical research. Clinical and laboratory research is conducted shoulder-to-shoulder at the Clinical Center and this tandem approach drives all aspects of its operations. (Also see "NIH Clinical Center" in the section on "Extramural and Intramural Research Programs" in Chapter 1)

Center for Information Technology (CIT). CIT incorporates the power of modern computers into NIH's biomedical and behavioral research programs and administrative procedures by focusing on three primary activities: conducting computational biosciences research, developing computer systems, and providing computer facilities. (Also see "Information and Information Technology" in the section on "Providing the Platform for Discovery" in Chapter 1.)

Center for Scientific Review (CSR). CSR carries out peer review of the majority of research and fellowship applications submitted to NIH; serves as the central receipt point for all such Public Health Service applications; makes referrals to scientific review groups for scientific and technical merit review of applications and to funding components for potential award; and develops and implements innovative, flexible ways to conduct referral and review for all grant applications. (Also see "NIH Peer Review Process" under the section on "Extramural and Intramural Research Programs" in Chapter 1.)

Office of the Director

Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI). DPCPSI was established by mandate of the NIH Reform Act of 2006. DPCPSI's role is to identify emerging scientific opportunities, rising public health challenges, and scientific knowledge gaps that merit further research; assist NIH in effectively addressing identified areas; and develop and apply resources (databases, analytic tools, and methodologies) that will support priority setting and analyses of the NIH portfolio. DPCPSI now incorporates the functions of the former Office of Portfolio Analysis and Strategic Initiatives. The primary components within DPCPSI are the Office of Strategic Coordination, which manages the NIH Common Fund (including the Roadmap), and the four OD program offices. DPCPSI also is the locus for NIH planning and reporting required by the Government Performance and Results Act and other government-wide performance assessment endeavors. (Also see the section on *NIH Strategic Planning and the NIH Roadmap and Common Fund* in Chapter 1).

As detailed below, the four OD Program Offices are in the areas of disease prevention; behavioral and social sciences research; women's health; and AIDS research.

- Office of Disease Prevention (ODP). ODP fosters, coordinates, and assesses research related to disease prevention and health promotion, and disseminates related information that aims to improve the health of the U.S. population. ODP advises the NIH Director and collaborates with other Federal agencies, academic institutions, the private sector, nongovernmental organizations, and international organizations in the formulation and implementation of research initiatives and policies that promote public health. There are three additional offices within ODP: Office of Rare Diseases Research (ORDR), Office of Dietary Supplements (ODS), and Office of Medical Applications of Research (OMAR):

    - ORDR stimulates, coordinates, and supports research on rare diseases to advance research opportunities and to respond to the needs of approximately 25 to 30 million people who have one of the approximately 6,500 known rare diseases. (Also see the section on the Rare Diseases Clinical Research Network in Chapter 4, which addresses NIH Centers of Excellence.)

    - ODS promotes and supports, through collaboration with the ICs, basic and clinical research to increase understanding of the impact of dietary supplements (e.g., plant extracts, enzymes, vitamins, minerals, amino acids, hormonal extracts) on disease prevention and health maintenance. The mission is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public.

    - OMAR is the focal point for evidence-based assessments of medical practice and state-of-the-science conferences key mechanisms for assessing, translating, and disseminating the results of biomedical research to improve the delivery of health services to the public. The office also conducts an annual course to train journalists on how to critically evaluate and report on medical research.

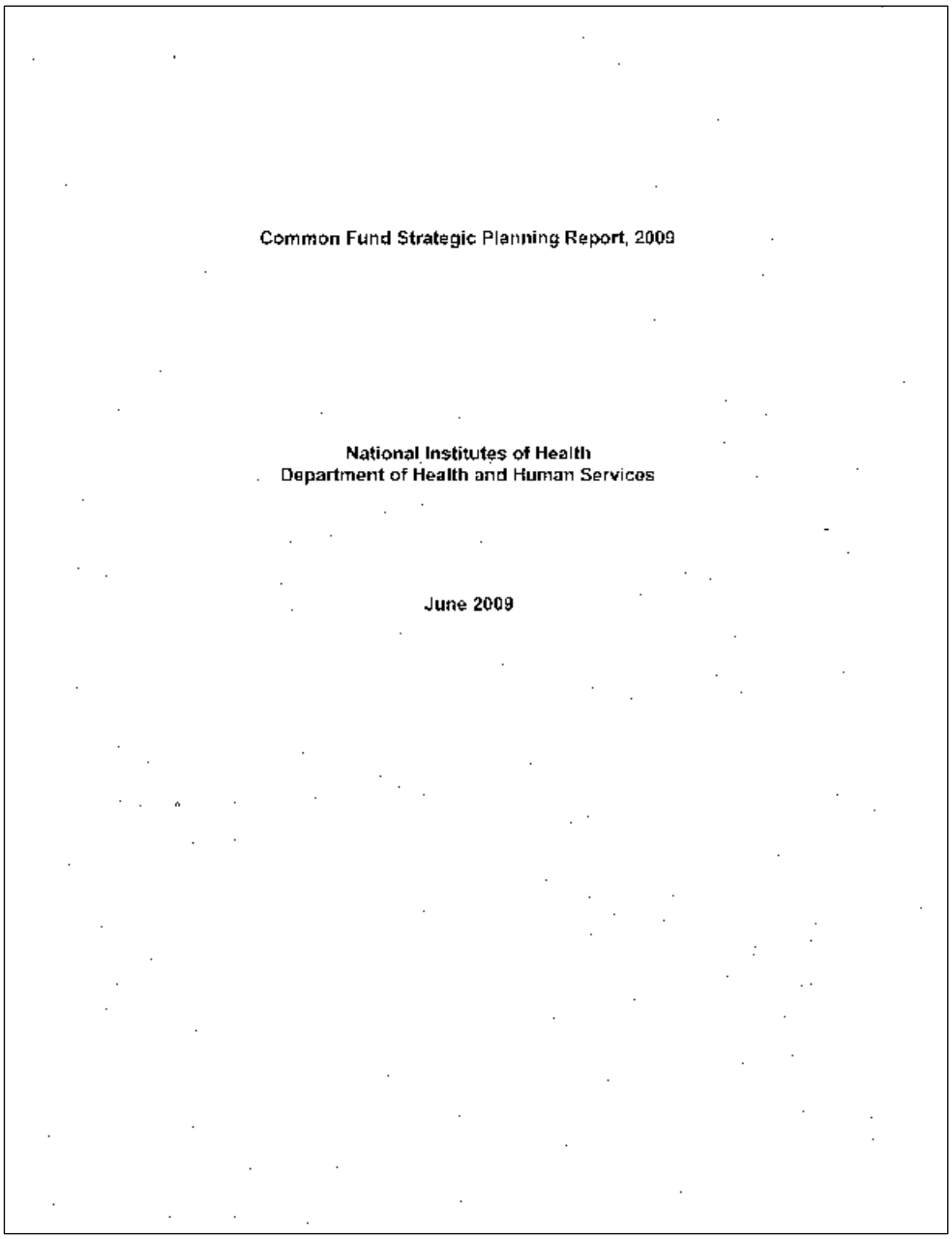
- Office of Behavioral and Social Sciences Research (OBSSR). OBSSR coordinates and stimulates behavioral and social sciences research throughout the NIH and integrates it more fully into the NIH research enterprise. The Office provides leadership on matters relating to research on the roles of human behavior and the social environment in the development of health, prevention of disease, and therapeutic intervention, as well as in training, continuing education, and dissemination of research findings to the broader scientific community and the general public.

- Office of Research on Women's Health (ORWH). ORWH serves as the focal point for women’s health research at NIH, and promotes, enhances, and expands efforts to improve the health of women through biomedical and behavioral research, including that on sex and gender factors. ORWH ensures compliance with policies on the inclusion of women and minorities in clinical research, and develops and implements NIH programs for the recruitment, retention, reentry, and advancement of women in biomedical careers.

- Office of AIDS Research (OAR). OAR is responsible for the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. Through its unique and comprehensive trans-NIH planning, budgeting, and portfolio assessment processes, OAR sets trans-NIH scientific priorities, enhances collaboration, and ensures that research dollars are invested in the highest priority areas of scientific opportunity that will lead to new tools in the global fight against AIDS. OAR also supports a number of initiatives to enhance dissemination of research findings to researchers, physicians, institutions, communities, constituency groups, and patients.

[1] With enactment of the Patient Protection and Affordable Care Act, on March 23, 2010, the National Center for Minority Health and Health Disparities became an institute–the National Institute for Minority Health and Health Disparities (NIMHD).

Appendix C: Common Fund Strategic Planning Report, 2009



Common Fund Strategic Planning Report, 2009

National Institutes of Health
Department of Health and Human Services

June 2009

Common Fund Strategic Planning Report, 2009

The National Institutes of Health Reform Act of 2006 requires the Secretary of Health and Human Services (HHS), acting through the Director of the National Institutes of Health (NIH), to submit a report to Congress containing a strategic plan for funding research that, "…represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that deserve special emphasis and would benefit from conducting or supporting additional research that involves collaboration between 2 or more national research institutes or national centers, or would otherwise benefit from strategic coordination and planning" (42 U.S.C. §282(b)(7)(a)).

To date, the Common Fund has been used to support research initiatives under the NIH Roadmap for Medical Research. The NIH Roadmap is an innovative approach to accelerate fundamental discovery and translation of that knowledge into effective prevention strategies and new treatments. The strategic initiatives funded under the NIH Roadmap address critical roadblocks and knowledge gaps that currently constrain rapid progress in biomedical research. They synergize the work of many NIH Institutes and Centers (ICs), and collectively represent a unique effort that no single or group of ICs or other entity can do, but are the responsibility of the NIH as a whole.

Initiatives under the Roadmap programs are intended to be catalytic in nature and are not expected to receive long-term Common Fund support. The intent with Roadmap programs is to stimulate the development of tools or technologies, acquire fundamental knowledge and data sets, or build critical research resources. The continued use of the tools, data, and resources is to be funded through the ICs.

Although the Roadmap programs are currently the only programs funded by the Common Fund, this may not always be the case as new scientific opportunities emerge and the NIH determines how best to respond to new challenges. As the Common Fund grows, the NIH will maintain a continuous effort to be responsive to community needs while providing ongoing support for areas identified through strategic planning endeavors.

This report describes:

- The strategic planning processes undertaken to date to identify program areas currently supported by the Common Fund
- The current status of programs designed to meet the needs articulated through strategic planning
- The plans for future strategic planning efforts

I. Strategic Planning for the Common Fund, 2002-2008: the NIH Roadmap

As described in the Common Fund Strategic Planning Report of 2007, the NIH Roadmap is a series of cross-cutting programs designed to meet criteria established by the NIH Leadership before the Common Fund was established through the 2006

Table 2: Common Fund/Roadmap Budget Data

Dollars in Millions	FY 2006 Actual B.A.	FY 2007 Actual B.A.	FY 2008 Actual B.A.	FY 2009 Enacted	2010 Request
Institute or Center Roadmap/ Common Fund Contribution	$247.3	$0.0	$0.0	$0.0	$0.0
OD Roadmap/Common Fund Contribution	$85.3	$483.0	$498.2	$541.1	$549.0
Roadmap/Common Fund	**$332.6**	**$483.0**	**$498.2**	**$541.1**	**$549.0**
Roadmap/Common Fund Percent of NIH Labor/HHS Budget Authority[1]	1.2%	1.7%	1.7%	1.8%	1.8%

[1] Adjusted for Type I Diabetes, Global Fund for AIDS, Superfund, and Secretary's transfer authority for NLM.

The status of each of the programs is described in further detail below.

1. Roadblock: Clinical and translational research lags behind basic discoveries.

Programs designed to overcome this problem: Clinical and Translational Science Awards (CTSAs), Clinical Research Training Program (CRTP), Medical Scientist Training Program (MSTP), Rapid Access to Intervention Development (RAID), Patient-Reported Outcomes Measurement Information System (PROMIS), and Clinical Research Policy Analysis and Coordination (CRPAC).

A. Clinical and Translational Science Award Program (CTSAs)

Status: This program supports a national consortium that provides a foundation for clinical and translational science that will catalyze clinical and translational research and allow investigators to move more quickly toward improvements in health. The program is jointly supported by the Common Fund and the National Center for Research Resources. The CTSA program affords the provision of research services and facilities, development of information systems that link clinical research centers nationwide, expansion of the national clinical research enterprise to include community clinics, and training a new generation of clinical investigators. This program, begun in 2006, is transitioning out of the Roadmap to be supported solely by NCRR in 2015.

B. Clinical Research Training Program (CRTP)

Status: As part of the Roadmap's effort to bolster the pipeline of clinical investigators, NIH's CRTP immerses medical students in an intense 12-month research experience during which they acquire the skills necessary to become successful, independent investigators and clinicians. The training environment of

the NIH campus fosters multidisciplinary approaches and provides access to unique patient populations via the largest hospital dedicated to clinical research in the world. This program, begun in FY 2004, is transitioning to full support by the NIH Clinical Center in FY 2014.

C. Rapid Access to Intervention Development (RAID)/Translational Research Core Services

Status: This program makes available, on a competitive basis, certain critical resources that are needed 1) for the development of therapeutic agents and 2) to bridge the gap between discovery and clinical testing to enable more efficient translation of promising discoveries. The RAID program is designed to reduce some of the common barriers that block progress of therapeutic discoveries, especially in cases where efforts involve high risk ideas or therapies for uncommon disorders that cannot attract private sector investment. Where private sector capacity for drug development is limited or not available, the NIH provides the resources needed to facilitate development of promising new therapies for widespread clinical use. By providing investigators with access to drug development resources, as well as expertise in the planning and submission of documents to the Food and Drug Administration (FDA), the RAID Program plays an integral role in fostering the development of novel therapeutics. This program is expected to be continued by IC funds when it transitions out of the Common Fund in FY 2014.

D. Patient-Reported Outcomes Measurement Information System (PROMIS)

Status: PROMIS is a revolutionary effort to enhance the measurement of patient-reported symptoms and functions. In the first phase of the program (FY 2004-2008), PROMIS developed and tested a large survey for measuring patient-reported outcomes and created a computerized adaptive testing system that analyzes all the responses and cross checks them against each other to gain a better understanding of the patient's well being. By analyzing the answers to multiple questions, the computerized adaptive testing system arrives at a more robust, quantifiable measurement of the patient's condition. The PROMIS Program has also created a publicly available, continually updated, Web-based system that allows clinical researchers to access PROMIS-validated items, domains, computerized adaptive testing, and survey forms. Preliminary results demonstrate that brief, 4- to10-question surveys of symptoms and functional states administered by the computerized adaptive testing outperforms today's commonly used, paper-based, self-reporting assessment tools in common health conditions. These results are indicative of the anticipated clinical research advantage of the PROMIS tool, which yields better answers with fewer patients. This program will be supported by the Common Fund through FY 2012, after which it is expected to be supported largely through public-private partnerships in support of clinical studies.

E. Clinical Research Policy, Analysis, and Coordination (CRPAC)

Status: This program was established to help catalyze the harmonization of clinical research policies across U.S. Government agencies. CRPAC engages relevant Federal agencies as well as private sector stakeholders to coordinate, streamline, and optimize policies and requirements for the conduct and oversight of clinical research. The multiple and often inconsistent Federal requirements governing biomedical research present a considerable challenge to the biomedical research community. To address this problem, CRPAC has led a major effort to enhance the consistency of regulatory requirements, facilitate compliance, and optimize the analysis and use of adverse event data. CRPAC has developed a Basal Adverse Event Report (BAER) tool, a single baseline set of medical information for reporting adverse events and unanticipated problems in clinical research that is acceptable to multiple Federal agencies. The BAER includes both pre- and postmarket reporting and complies with national and international standards for data transmission and vocabularies. This program, established through the Office of Science Policy (OSP), NIH Office of the Director (OD), is transitioning out of the Roadmap to become a permanent activity within OSP in FY 2010.

2. Roadblock: Partnerships between NIH and private sector entities can be difficult to cultivate and maintain.

Program designed to overcome this problem: Public-Private Partnerships (PPP)

Status: This program was developed as part of NIH's efforts to facilitate new ways of conducting and supporting research, including the formation of collaborations with pharmaceutical and biotechnology industries, as well as other private entities. The program identifies appropriate partners inside and outside the NIH, as well as develops useful policies to oversee those partnerships. As part of this program, the NIH has established the Biomarkers Consortium, a complex group of related partnerships between the NIH, FDA, industry, and private entities that work to accelerate the development of new drugs by identifying, developing, and qualifying biomarkers, useful indicators of disease progression and effects of therapeutic interventions. This program, established through the OSP in the NIH OD, is transitioning out of the Roadmap to become a permanent activity within OSP in FY 2010.

3. Roadblock: Traditional R01 application and review processes can hamper innovation.

Programs designed to overcome this problem: High Risk High Reward Programs, including the NIH Director's Pioneer Program, NIH Director's New Innovator Program, and Transformative R01 Program.

Status: The High Risk High Reward component of the NIH Roadmap has been built with the intent of finding new ways to foster innovation by piloting new application and review processes. The Common Fund, through these programs, sets aside a small

percentage of the overall NIH budget for transformative research without designating specific funding levels for specific scientific areas. All areas compete, with the most innovative proposals receiving the funds.

A. NIH Director's Pioneer Awards

Status: This program seeks to identify individual investigators with a proven history of innovation and provide them with adequate funding to conduct pioneering research in a new area of investigation. It provides funding for scientists who propose innovative approaches that have the potential to produce an unusually high impact on a broad area of biomedical or behavioral research. The awardees propose to use pioneering and transformative approaches to address major scientific problems and challenge existing paradigms. Since 2004, the program has supported 63 individual investigators. Information about this program, as well as links to awardees by year, can be found at http://nihroadmap.nih.gov/pioneer/. This program has proven to be successful at the identification of outstanding scientists and innovative projects and receives funds from both the Common Fund and various ICs. The NIH Director therefore decided to continue Common Fund support for the program for the foreseeable future.

B. NIH Director's New Innovator Awards

Status: This program supports new investigators who propose research ideas that are unusually creative and highly innovative but lack the preliminary data required to apply for an RO1 grant. Since 2007, this program has supported 61 individual investigators. Information about this program, as well as links to awardees by year, can be found at http://nihroadmap.nih.gov/newinnovator/. Launched in response to Congressional language, this program, like the NIH Director's Pioneer Awards Program, is projected to continue with combined funding from the ICs and the Common Fund for the foreseeable future.

C. Transformative R01s

Status: A new program for 2009, this program is intended to allow investigators to articulate pressing needs or areas of opportunity and to fund the most transformative of these projects. Whereas the Pioneer Awards Program emphasizes the past history of the individual investigator, the Transformative R01 Program emphasizes the potential impact that each project may have. It encourages the formation of teams to accomplish the goals of the program and provides adequate funds to support complex projects. This program will pilot a new way of encouraging very high impact research by removing as many administrative barriers as possible. No budget cap is imposed, allowing maximum flexibility to investigators to develop complex approaches that may be beyond the budget of traditional R01s. Award decisions are made by the NIH Director based upon recommendations from a multidisciplinary group of outside experts. Areas of

highlighted need have been identified through the Roadmap Strategic Planning Process, but these awards are open to all areas of investigation and no set-aside dollar figure has been established for any particular topic. If the areas of highlighted need are not adequately addressed through this program, future initiatives on these topics may be developed.

These areas include:

a) Understanding and Facilitating Human Behavior Change
b) Complex 3-Dimensional Tissue Models
c) Formulation of Novel Protein Capture Reagents
d) Providing an Evidence Base for Pharmacogenomics
e) Functional Variation in Mitochondria in Human Disease
f) Transitions from Acute to Chronic Pain

4. Roadblock: Interdisciplinary approaches to complex scientific problems can be difficult to develop.

Program designed to overcome this problem: Interdisciplinary Research (IR) Program

Status: This program overcomes barriers to interdisciplinary research by building research teams, training scientists in multiple disciplines, and changing academic research culture. The program includes initiatives to dissolve academic department boundaries within academic institutions and increase cooperation between institutions, train scientists to cultivate interdisciplinary efforts, and build bridges between the biological sciences and the behavioral and social sciences.

A total of nine IR consortia, managed by teams of NIH staff from multiple ICs, have been funded through this initiative, which represents a new funding mechanism for interdisciplinary research. Through this mechanism, the NIH is piloting a new way to fund projects that cross IC missions and require cooperation among NIH staff to manage the programs. These consortia address complex problems that require novel, interdisciplinary approaches, including aging, fertility in women who undergo cancer therapy, regenerative medicine, Fragile X Syndrome, neuropsychiatric disorders, obesity, genetic engineering strategies, stress and its effects on self control and addiction, and genomics-based drug discovery. Funded in FY 2007, these consortia will be funded by the Common Fund through FY 2011. If the new funding mechanism proves worthwhile, it may continue to be utilized through IC funds for either new projects or for continuation of the existing Common Fund-initiated projects.

As part of the IR Program's efforts, the Interdisciplinary Health Research Training Program enables institutions to develop postdoctoral training programs that provide formal coursework and research training in a new interdisciplinary field to individuals holding advanced degrees in different disciplines. Another IR program, entitled Training for a New Interdisciplinary Workforce, supports scientists at the undergraduate,

graduate, and postdoctoral levels by exposing them to both didactic and research experiences involving interdisciplinary and team approaches to address complex biomedical problems. These training programs, launched in FY 2004, will compete for IC funds with IC-specific training programs beginning in FY 2009.

In an effort to help bridge the gap between medical researchers and behavioral or social scientists, the IR Program also provides exploratory/developmental grants through the Methodological and Technological Innovation in the Behavioral and Social Sciences Program to help facilitate the introduction of new methodologies and technologies to the behavioral and social sciences. These projects, funded in FY 2007, followed workshops held to foster team building in FY 2004 and FY 2006.

Finally, the IR Program encourages changes to administrative practices at NIH in ways that encourage teamwork through recognition and support of team leadership. Working with the NIH Office of Extramural Research, members of the trans-NIH IR Working Group helped design and implement the policy through which NIH now recognizes multiple principal investigators on individual projects. The recognition of multiple principal investigators represents a transformative step through which NIH seeks to foster collaboration and teamwork.

5. Roadblock: Small molecular compounds are needed to explore functions of human genes and to serve as leads for therapeutic compounds that can modify activity.

Program designed to overcome this problem: Molecular Libraries and Imaging Program

Status: This program establishes a national network of centers and supporting technologies for the discovery and development of small molecule probes to interrogate and modify biological pathways. The program currently supports a network of research centers that have identified new "probes"–molecules that are useful for research purposes and could be adapted for therapeutic use. Experts at the centers optimize and perform assays designed by academic researchers and peer-reviewed by the NIH. The centers use advanced technology to screen thousands of small molecules for their ability to bind to or inhibit a protein or protein-mediated activity of interest. In collaboration with the academic scientists who designed the assays, the center validates the "hits" and chooses a subset to improve by chemical modification. To date, the program has assembled a variety of screening assays designed to test small molecules for their ability to target proteins in critical cellular processes such as cellular transport, enzymatic reactions, and protein-protein interactions that become anomalous in multiple diseases. The screening center program moved from its pilot phase to its production phase in FY 2008 and will be funded by the Common Fund through FY 2013, with cofunding from the ICs beginning in FY 2012. It is expected to transition exclusively to IC support beginning in FY 2014.

To support this large scale screening program, several support programs were developed as part of the pilot phase of the program and are continuing during the

production phase. An assay development program, which funds investigators to develop high throughput screening assays for their biological area of interest, has been critical for enabling investigators to take advantage of the resources offered by the screening center. A technology development program enabled improvements to be made to the technical aspects of the high throughput screening process. In addition, an informatics component has been critical for the centralized collection of information about the molecules screened, their structures, and their activities in various assays; for allowing public access to this information; and for development of new informatics methodologies to mine the data. Finally, the library of compounds that the program has developed represents a truly unique and valuable component of the program as a whole. This collection is expected to grow from 300,000 to 500,000 compounds over the next 5 years. These components, which support the screening endeavor, are anticipated to transition to IC funding in FY 2014.

In addition to the small molecule screening effort, this program supports initiatives that are intended to develop novel imaging probes–in part, through adaptation of molecules that could be identified as probes through the screening centers. These initiatives have developed a database of imaging reagents and have supported the development of novel imaging reagents. Common Fund support for the database continues through FY 2013, while future funding for the imaging probe synthesis facility will be determined later this year.

6. Roadblock: A scientific gulf exists between basic nanotechnology research and clinical applications.

Program designed to overcome this problem: Nanomedicine

Status: This program establishes a network of Nanomedicine Centers to determine how cellular machines operate at the nanoscale level and use these design principles to develop and engineer new technologies and devices for repairing tissue, as well as preventing and curing diseases. Launched in FY 2005, the program's first five years were intended to address fundamental basic science questions as a prerequisite to the development of therapeutic strategies. To achieve the targeted goals of this program, the NIH uses flexible authority (Section 214 of the Appropriations Law) to oversee and manage the research. This authority facilitates the movement of funds to the most successful projects within the program. Approved for its second five-year funding period this past year, the program is now planned to continue with Common Fund support through FY 2014. This is a high risk program that expects the goals, if accomplishable, can be achieved within an overall 10-year timeframe of the program.

7. Roadblock: Limited technologies to analyze protein-protein interactions and cellular pathways hinder therapeutic applications.

Program designed to overcome this problem: Building Blocks, Biological Pathways, and Networks

Status: This program consists of two initiatives that are intended to catalyze basic studies of cellular functions by developing tools that will allow basic scientists to study protein-protein interactions and to analyze the consequences of cellular activities through examination of cellular metabolites.

The Technology Centers for Networks and Pathways develop and apply technologies to detect transient protein-protein interactions that control the cellular functions. Five centers were established in FY 2005 to develop innovative tools to enable researchers to determine, in real time, the amounts, locations, and interactions of large numbers of individual proteins within a single cell. These fundamental needs are still pressing and unsolved, so these centers will receive additional support through the Common Fund through FY 2013.

The Metabolomics initiative was established in FY 2004 to support the development of technologies that will allow investigators to monitor cellular processes more accurately through analysis of by-products (metabolites) generated by the processes. This program was developed as a 5-year program that has been jointly funded by the Common Fund and the ICs. FY 2008 was the last year of Common Fund support for this initiative, as IC-funded investigators can now use the technologies developed, and further technical advances are being funded through the ICs.

8. Roadblock: Limited technologies for structural analysis of membrane proteins can limit drug development.

Program designed to overcome this problem: Structural Biology of Membrane Proteins

Status: This program establishes centers for Innovation in Membrane Protein Production as well as individual research projects that aim 1) to formulate new methods for producing ample quantities of cellular membrane proteins that are of a quality suitable for structural and functional studies and 2) to develop and improve technologies and methods for structural analysis. The program develops novel approaches for the production and stabilization of membrane proteins to enable determination of their structures at high resolution. These approaches are paying off, as increasing numbers of membrane-associated protein structures are being determined and facilitating drug development. The success of the protein and continued need for technology development in this area prompted the decision to fund this program for an additional 5 years through the Common Fund; funding is now expected to continue through FY 2013. After that point, the community at large is expected to use the new technologies to analyze membrane proteins and use this knowledge to design novel therapies.

9. Roadblock: Computational tools that allow investigators to mine large datasets need to be developed and combined into an integrated network.

Program designed to overcome this problem: National Centers for Biomedical Computing (NCBCs)

Status: This program was established in 2004 to develop computational tools intended to catalyze research in the basic and clinical sciences. The centers create innovative software programs and other tools that arm the biomedical community with the methods needed to integrate, analyze, model, simulate, and share data relevant to human health and disease. Each center also works with members of the research community to develop informatics needs targeted toward specific disease areas. These "driving biological problems" include Huntington's Disease, Hypertension, Cardiovascular Disease, Alzheimer's Disease, Diabetes, Schizophrenia and Bipolar Disorder, HIV, Prostate Cancer, and heritable disorders. The set of disease areas targeted by these efforts is dynamic and responsive to needs of the community. The need for informatics is so broad and cross-cutting that this program is continuing with Common Fund support through FY 2014.

10. Roadblock: Knowledge of the contribution of nonpathogenic microbes to human health is rudimentary but could potentially transform our understanding of health and disease.

Program designed to overcome this problem: Human Microbiome Project

Status: This program develops tools and generates resources to facilitate characterization of the human microbiome and analysis of its role in human health and disease. The program establishes links between the human microbiome and states of health and disease through several integrated initiatives.

The first was launched in FY 2007 to "jumpstart" the effort by sequencing a reference set of genomes from cultured microbes. These reference sequences will facilitate the analysis of complex mixtures of microbes to be obtained from human body sites. Beginning in FY 2009, samples from 5 body sites (skin, nose, mouth, gastrointestinal tract, and vagina) will begin to be collected from more than 100 individuals. By analyzing microbial populations at multiple body sites in normal, healthy individuals, the program builds the foundation for an advanced understanding of the degree of microbial diversity that may exist among individuals. A series of demonstration projects will build upon this foundation to analyze the microbiome in individuals with varying diseases or conditions to determine whether changes in our microbiome correlate with changes in health status.

In addition to the sequencing effort, this program supports the development of technological improvements that will enable the effort to proceed faster and with reduced costs. NIH is also working with researchers from several countries to establish the International Human Microbiome Consortium. This consortium will provide a forum for data sharing and information exchange relevant to the program. In addition, the vast amount of sequence data generated by this program will be deposited in a publicly accessible database and the sequences of the bacterial strains studied will be made available for future studies. Finally, the Ethical, Legal, and Social Implications (ELSI) of the microbiome project are being studied through a dedicated initiative.

The Human Microbiome Project will be funded by the Common Fund through FY 2012. During this timeframe, a foundation will be laid to allow the continued exploration of the human microbiome through investigator-initiated projects funded by the ICs.

11. Roadblock: Contributions of higher order DNA structure to human health and disease are poorly understood.

Program designed to overcome this problem: Epigenomics of Human Health and Disease

Status: This program seeks to help define the relationship between the modifications to DNA that alter its three-dimensional structure (the epigenome) and human health and disease. Like the Human Microbiome Project, a series of integrated initiatives has been established to achieve this goal.

Studies in experimental animal models has established that diet, environmental exposures, and aging can significantly alter genetic activity by producing chemical modifications to DNA that alter the coiled structure that DNA assumes in different cell types. However, very little information is available about the way that DNA coils in normal, healthy human cells, so it is difficult to know the extent to which human disease may result from changes to this structure. To clarify this, the Epigenomics Program is enabling the development of comprehensive reference maps of the human epigenome from many different cell types. It also fosters new technologies for epigenomic analysis, an integrated Data Coordinating Center, and novel regulators of epigenomic structure.

An understanding of the human epigenome has the potential to transform knowledge about disease onset and progression, as well as to lead to novel therapeutic approaches. Together with several international partners, the NIH is working to establish an International Consortium to foster collaboration and information exchange worldwide in this endeavor. The fundamental knowledge obtained through this program will catalyze research in all areas of medicine and increase our understanding of the genetic basis of health and disease. This program was launched with "jumpstart" funds in FY 2007 but major funding began in FY 2008. It is slated to receive Common Fund support through FY 2015.

12. Roadblock: Genome-Wide Association Studies reveal genetic variations that associate with disease, but the molecular effects of the variations is difficult to unravel.

Program designed to overcome this problem: Genotype/Tissue Expression (GTEx) Resource

Status: Genome-Wide Association Studies are revealing increasing numbers of genetic variations that result in susceptibility to disease. However, using this information to intercede before disease develops will require an understanding of the molecular consequences of the genetic variation. This is very difficult to unravel, since

a change in DNA sequence may alter a part of the chromosome involved in regulating a gene (or genes) far removed from the sequence variant itself, and it could influence the regulation of genes in many tissues.

To overcome this problem, the GTEx program, to begin in FY 2010, will correlate genetic variability with variability in expression of many genes in many tissues. To do this, samples from 320 donors (either surgical donors or autopsy donors) will be acquired from several tissues, the genotypes determined for each, and then a gene expression profile obtained for each tissue. The genes expressed and the level at which they are expressed can then be correlated with genetic variations of the donors.

Common Fund support of this program will allow the feasibility of the approach to be determined through a two-year period of support. Analysis of the data from the initial two years will determine whether further investment to scale up the approach is warranted.

III. Looking to the Future: Strategic Planning for the Common Fund

The Common Fund was established by the 2006 Reform Act to encourage strategic planning for research that crosses IC borders and coordination in program management. These core principles for the Common Fund are sufficiently broad that they provide the NIH with flexibility to determine the most pressing needs and to respond corporately to these challenges.

Through the Roadmap Programs, the NIH addresses fundamental, cross-cutting challenges that influence virtually every disease area and have potential for exceptionally high impact. Future planning for Roadmap programs will continue to involve heavy input from the public to identify common bottlenecks and to articulate cross-cutting areas of exceptional opportunity. However, as the Common Fund grows, additional types of programs may be supported that serve the stated mission of the Common Fund to encourage multi-IC planning and coordination but do not address the criteria established for the Roadmap.

While growth and diversification of Common Fund programs will depend on growth of the Fund itself, the planning strategies for all types of Common Fund programs will share the requirement that multiple ICs and their respective communities are served by each program. This will require staff from multiple ICs to interact, share information, and bring their communities together to identify gaps in knowledge, brainstorm, and articulate programmatic needs.

Facilitated by the Office of Strategic Coordination within the Division of Program Coordination, Planning, and Strategic Initiatives, these planning activities will involve gathering input at multiple levels to establish priorities for Common Fund dollars. Data concerning the NIH research portfolio, research conducted elsewhere, and the research needs vocalized by the community will also be used to help establish these priorities.

Appendix 1: Criteria for NIH Roadmap Programs

The overarching goal of all Roadmap initiatives is to accelerate the discovery and translation of scientific knowledge into public health benefits. Roadmap is conceived of as a five- to ten-year "incubator space" for NIH initiatives that meet all of the following criteria:

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?

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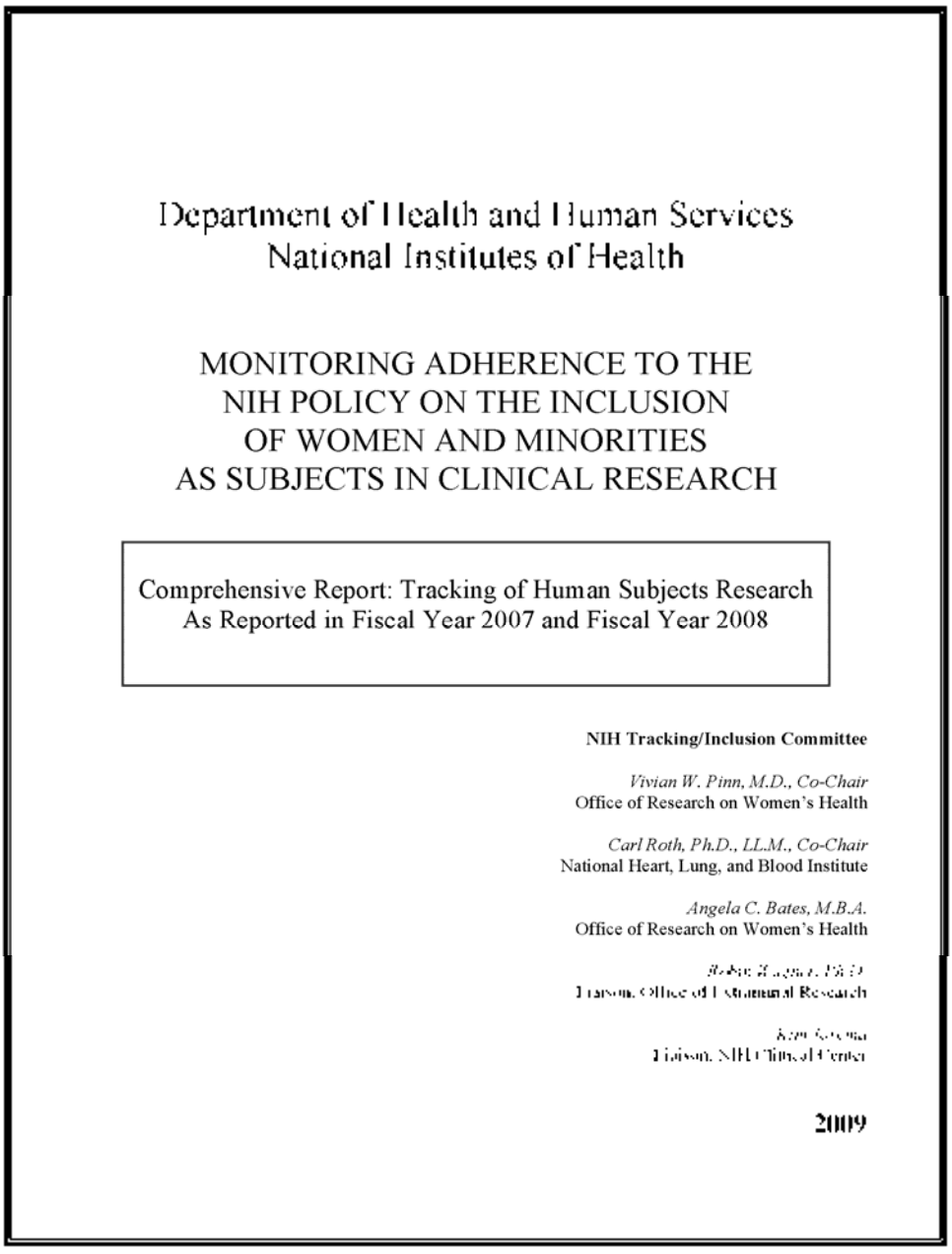
Appendix D: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research (excerpt)

Link to on-line version of full report can be found at
http://orwh.od.nih.gov/inclusion/2009AnnualTrackingInclusionComprehensiveRpt.pdf



Department of Health and Human Services
National Institutes of Health

MONITORING ADHERENCE TO THE
NIH POLICY ON THE INCLUSION
OF WOMEN AND MINORITIES
AS SUBJECTS IN CLINICAL RESEARCH

Comprehensive Report: Tracking of Human Subjects Research
As Reported in Fiscal Year 2007 and Fiscal Year 2008

NIH Tracking/Inclusion Committee

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2009

Preface

To demonstrate effective implementation of Public Law 103-43 and implementation of NIH policies on the tracking and inclusion of women and minorities in clinical research, the Office of Research of Women's Health (ORWH), in collaboration with the Office of Extramural Research (OER) and the Office of Intramural Research (OIR), has led monitoring efforts for compliance including convening a trans-NIH Tracking and Inclusion Committee. Monitoring efforts have included the documentation of the numbers of males and females by race and ethnicity enrolled in clinical studies funded by NIH, as well as biennial statements from each Institute and Center (IC) Advisory Councils to confirm compliance with NIH policies. These and other efforts serve to ensure that NIH procedures comply with the NIH policy on the inclusion of women and minorities in clinical studies.

Data monitoring for the magnitude and diversity of clinical studies funded by NIH is not a simple task. There has been an extensive and dedicated effort to provide accurate and reproducible data. However, transitions in information system software at the NIH have introduced the need for modifications for monitoring inclusion and data collection.

The Acting Director of NIH has now established a task force to be co-chaired by the Director of ORWH, the Director of the National Center for Minority Health and Health Disparities (NCMHD), and an IC Director to examine the entire process for evaluating and monitoring the inclusion of women and minorities in clinical research funded by NIH; and the results of the deliberations of this task force should be reflected in the next biennial report. However, the FY2007 and FY2008 data in this document reflect the data reporting and current trends of the inclusion of participants in NIH clinical research.

This report would not be possible without the efforts of the members of the NIH Tracking and Inclusion Committee and the eRA Population Tracking User Group (ePTUG) who have each provided many hours addressing a multiplicity of issues related to data entry, reconciliation of grants, contracts and cooperative agreements, and other related issues or concerns.

Appendix D: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research (excerpt)

Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research
Summary Report of NIH Inclusion Data

NIH AGGREGATE POPULATION DATA REPORTED IN FY2007 and FY2008

Because new clinical research studies begin each year while other studies may be ending, the inclusion figures will vary from year to year due to the scientific topics under study and the prevalence of those conditions within each individual study. These data help to establish trends on the inclusion of women and minorities as subjects in clinical research. Data on inclusion are tabulated from human subject populations in NIH-defined Phase III clinical trials and other human subject research studies and are based on self identification by the participants. NIH clinical research studies are determined in accordance with the NIH definition of clinical research to include, for example, non-intervention clinical research, non Phase III clinical trials, epidemiological studies, behavioral studies, and database studies.

Analysis of aggregate NIH data on inclusion for FY2007 and FY2008 documents participants of all ages, that substantial numbers of women and men, non-minority men, and minorities of all ages have been included as research subjects in NIH clinical trials and other human subject research studies during these fiscal years. However, caution should be utilized to avoid over-interpreting the figures that are provided. The NIH Tracking and Inclusion Committee have provided for the reader's interest conclusions that can be reasonably drawn from the data.

Previous inclusion reports and aggregate enrollment figures for women, men and minority groups for FY1994 to the present can be found on the ORWH website at http://orwh.od.nih.gov/inclusion.html.

NIH CLINICAL RESEARCH: Fiscal Years 2007 and 2008

In FY2007 there were 15,567 extramural and intramural clinical research protocols, including Phase III and other clinical studies, of which 10,914 protocols reported human subject participation as noted in this report's trend summary tables *(Table 1A)*. Of these, 95.9% were domestic protocols and 4.1% were foreign protocols. *(Table 1E)* Approximately 17.4 million participants were enrolled in extramural and intramural research protocols of which 92.7% were domestic participants and 7.3% were foreign participants. Of the 17.4 million participants, 58.2% were women, 39.5% were men and 2.3% did not provide sex identification.*(Table 1A)* Further, 29.9% of the total participants, and 26.5% of the Domestic-only participants, were reported as minorities following the current OMB categories for race and ethnicity. (*Table 1F and 2C)*

Correspondingly, in FY2008 there were 15,598 extramural and intramural clinical research protocols, including Phase III and other clinical studies, of which 11,045 protocols reported human subject participation as noted in this report's trend summary tables.*(Table 1A)* Of these, 95.5% were domestic protocols and 4.5% were foreign protocols.*(Table 1E)* Approximately15.4 million participants were enrolled in extramural and intramural research protocols of which 91.7% were domestic participants and 8.3% were foreign participants. Of the 15.4 million participants, 60.4% were women, 38.9% were men and 1.1% did not provide sex identification.*(Table 1A)* Further 28.6% of the total participants, and 24.9% of the Domestic-protocol participants, were reported as minorities following the current OMB categories for race and ethnicity. *(Table 1F & Table 2C)*

While the number of participants in all extramural and intramural clinical research decreased (17.4%) in FY2007 and 15.4% in FY2008), there was no significant change in the proportion of women and men (58.2%F and 39.5%M in FY2007; and 60.0%F and 38.9%M in FY2008). *(Table 1A)*

NIH Defined Phase III Clinical Research: FY2007 and FY2008

In FY2007 there were 749 extramural and intramural Phase III clinical research protocols, of which 653 protocols reported human subject participation as noted in this report's trend summary tables.*(Tables 4A and 5A)* Of these, 93.3% were domestic protocols and 6.7% were foreign protocols. Clinical studies not included in this analysis are those studies that have just begun and have not reported enrollment data or have not begun recruiting patients. *(Table 4A)* A total of 591,159 participants were enrolled in extramural and intramural Phase III research protocols of which 72.5% were domestic participants and 27.5% were foreign participants. Of the 591,159 participants, 54.9% were women, 42.2% were men and 2.8% did not provide sex identification. *(Table 4A)* Further, 41.4% of the total participants, and 20.6% of Domestic-protocol participants, in Phase III clinical research were reported as minorities following the current OMB categories for race and ethnicity. *(Table 5C)*

Of the 197 extramural and intramural Phase III research protocols that report following the former OMB standards in FY2007, minority representation was highest for Blacks (not Hispanic) at 10.3% and lowest for American Indian Alaska Natives at 0.4%. Hispanics represented approximately 4.5%. Asian Pacific Islanders were 1.9% and Whites (not Hispanic) 81.0% of the participants. The categories *Hawaiian Pacific Islander* and *More Than One Race* were not designations with the former OMB standards *(Table 4B)*

Moreover, in FY 2007, there were 424 extramural and intramural Phase III research protocols reporting data following the current OMB standards for reporting by both race and ethnicity. Accordingly, minority representation by race was highest for Blacks at 22.1% and lowest for Hawaiian Pacific Islanders 0.1%. Asians represented 12.4%, American Indian Alaska Natives 2.5% and Whites 34.9% of participants. Participants identifying as *More Than One* Race were 1.1% of the total number of participants. In addition, 26.9% did not identify a race category *(Table 4C)*. Of the 424 extramural and intramural Phase III research protocols designating an ethnicity in FY2007, 66.8 % of total participants identified as "Not Hispanic", 18.8 % of the total participants identified as "Hispanic or Latino", and 14.5% of the total participants did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately. *(Table 4D)*

Correspondingly, in FY2008 there were 726 extramural and intramural Phase III clinical research protocols, of which 639 protocols reported human subject participation as noted in this report's trend summary tables. *(Tables4A and 5A)* Of these, 91.5% were domestic protocols and 8.5% were foreign protocols. Clinical studies not included in this analysis are those studies that have just begun and have not reported enrollment data or have not begun recruiting patients. A total of 792,578 participants were enrolled in extramural and intramural Phase III research protocols of which 74.6% were domestic participants and 25.4% were foreign participants.*(Table 4A)* Of the 792,578 participants, 57.5% were women, 40.3% were men and 2.2% did not provide sex identification.*(Table 4A)* Further, 38.9% of the total participants, and 20.2% of Domestic-only participants, in Phase III clinical research were reported as minorities following the current OMB categories for race and ethnicity. *(Table 5C)*

Of the 164 extramural and intramural Phase III research protocols that report following the former OMB standards in FY2008, minority representation was highest for Blacks (not Hispanic) at 9.7% and lowest for American Indian Alaska Natives at 0.4%. Hispanics represented approximately 4.1%. Asian Pacific Islanders were 2.6% and Whites (not Hispanic) 82.0% of the participants. The categories *Hawaiian Pacific Islander* and *More Than One Race* were not designations with the former OMB standards *(Table 4B)*

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Moreover, in FY 2008, there were 475 extramural and intramural Phase III research protocols reporting data following the current OMB standards for reporting by both race and ethnicity. Accordingly, minority representation by race was highest for Blacks at 18.4% and lowest for Hawaiian Pacific Islanders 0.1%. Asians represented 17%, American Indian Alaska Natives 2.7% and Whites 50.2% of participants. Participants identifying as *More Than One Race* were 2.2% of the total number of participants. In addition, 9.4% did not identify a race category. Of the 475 extramural and intramural Phase III research protocols designating an ethnicity in FY2008, 82.3 % of total participants identified as "Not Hispanic", 11.5 % of the total participants identified as "Hispanic or Latino", and 6.2% of the total participants did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately. *(Table 4C)*

While the number of participants in Phase III extramural and intramural clinical research increased (591,159 in FY2007 and 792,578 in FY2008), there was a slight change in the proportions of women and men (54.9%F and 42.2% in FY2007 and 57.5%F and 40.3%M in FY2008) *(Table 4A)*

The following sections provide data on extramural research and intramural research separately.

EXTRAMURAL CLINICAL RESEARCH: Fiscal Years 2007 and 2008

In FY2007, there were 13,719 extramural clinical research protocols, including Phase III and other clinical studies, of which 9,362 protocols reported human subject participation. Of these, 82.3% were domestic protocols and 3.5% were foreign protocols. *(Table 7A)* Approximately 13.9 million participants were enrolled in extramural research protocols of which 92.8% of the total enrollment is domestic participants and 7.2% of the total enrollment is foreign participants. *(Table 7B)* Of the 13.9 million participants, 61.80% were women, 35.54% were men and 2.62% did not provide sex identification. Further, 31.44% of the total participants were reported as minorities following the current OMB categories for race and ethnicity. *(Table 8A)*

Correspondingly, in FY2008, there were 14,015 extramural clinical research protocols, including Phase III and other clinical studies, of which 9,381 protocols reported human subject participation. Of these, 81.2% were domestic protocols and 3.7% were foreign protocols. *(Table 9A)* Approximately 12.6 million participants were enrolled in extramural research protocols of which 91.7% of the total enrollment is domestic participants and 8.3% of the total enrollment is foreign participants. *(Table 9B)* Of the 12.6 million participants, 63.84% were women, 35.04% were men and 1.12% did not provide sex identification. Further, 29.4% of the total participants were reported as minorities following the current OMB categories for race and ethnicity. *(Table 10A)*

While the number of participants in extramural clinical research protocols decreased (13.9 million in FY2007 and 12.6 million in FY2008), there was no significant change in the proportions of women and men (61.8%F and 35.5%M in FY2007 and 63.8%F and 35.0%M in FY2008). *(Table 8A and Table 10A)* However, when sex-specific studies were excluded, the proportions of women and men in all extramural clinical research reported in FY2008 were similar to the proportions in the general population reported in FY2009 (from 46.5% to 45.61% for females and 49.8% to 52.6% for males. *(Table 11A and Table 12A)*

NIH Defined Phase III Extramural Clinical Research: FY2007 and FY2008

In FY2007 there were 711extramural Phase III clinical research protocols, of which 617 protocols reported human subject participation *(Table 13A)*. A total of 547,687 participants were enrolled in extramural Phase III research protocols of which 55.10% were women, 41.83% were men and 3.07% did not provide sex identification. *(Table 14A)*

In FY2007 there were 399 extramural Phase III research protocols reporting data following the current OMB standards for reporting race and ethnicity. Minority representation by race was highest for Blacks at 23.21% and lowest for Hawaiian/Pacific Islanders 0.13%. Asians represented 13.09%, American Indian/Alaska Natives 2.59% and Whites 34.29% of participants. Participants identifying as *More Than One* Race were 1.02% of the total number of participants. In addition, 25.7 % did not identify a race category. Of the 399 extramural Phase III research protocols designating an ethnicity in FY 2007, 67.77 % of total participants identified as "Not Hispanic", 17.78% of the total participants identified as "Hispanic or Latino", and 14.44 % of the total participants did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately. (*Table 14B*)

In FY2008 there were 696 extramural Phase III clinical research protocols, of which 602 protocols reported human subject participation. *(Table 15A)* A total of 776,034 participants were enrolled in extramural Phase III research protocols of which 57.22% were women, 40.58% were men and 2.2% did not provide sex identification. *(Table 16A)*

Correspondingly in FY2008, there were 452 extramural Phase III research protocols reporting data following the current OMB standards for reporting race and ethnicity. Minority representation by race was highest for Blacks at 18.68% and lowest for Hawaiian/Pacific Islanders 0.12%. Asians represented 17.41%, American Indian/Alaska Natives 2.74% and Whites 51.22% of participants. Participants identifying as *More Than One* Race were 2.22% of the total number of participants. In addition, 7.62 % did not identify a race category. Of the 452 extramural Phase III research protocols designating an ethnicity in FY 2008, 83.84 % of total participants identified as "Not Hispanic", 10.38% of the total participants identified as "Hispanic or Latino", and 5.78 % of the total participants did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately. (*Table 16B*)

While the number of extramural Phase III clinical research protocols decreased (711 in FY2007 and 696 in FY2008) *(Table 13A and Table 15A)*, there was a slight increase in the proportion of women (55.1 %F and 41.8%M in FY2007 and 57.2%F and 40.6%M in FY2008). *(Tables 14A and 16A)*

INTRAMURAL CLINICAL RESEARCH: Fiscal Years 2007 and 2008

In FY2007 there were 1,848 intramural clinical research protocols, including Phase III and other clinical studies, of which 1,552 protocols reported human subject participation. *(Table 7A)* Approximately 3.5 million participants were enrolled in intramural research protocols of which 43.39% were women, 55.42% were men and 1.20% did not provide sex identification. (*Table 16A*)

In FY2007, approximately 3.5 million participants were reported in all intramural research including Phase III clinical trials, and other clinical studies. Of the 449 intramural research protocols that report data following the former OMB standards, minority representation was highest for Blacks (not-Hispanic) at 17.6% and lowest for American Indian/Alaska Natives at 0.2%. Asian/Pacific Islanders represented 3.65%, Hispanics 4.31%; and Whites (not Hispanic) 73.16% of the intramural research study population. The categories *Hawaiian/Pacific Islander* and *More Than One Race* were not designations with the former OMB standards. (*Table 17C*)

For the 1,103 intramural clinical research studies that reported data following the current OMB standards in FY 2007, the largest racial minority group was Blacks at 9.72 % and the smallest racial minority group was Hawaiian/Pacific Islanders at 0.16%. Asian represented 7.66%, American Indian/Alaska Natives 0.89% and Whites 69.85% of participants in all intramural clinical research. Approximately 0.56% of participants reported *More Than One Race* as their racial category. In addition, 11.16 % did not identify a

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race category. Of the 1,103 intramural research protocols following the current OMB standards designating an ethnicity in FY2007, 85.50 % of total participants identified as "Not Hispanic", 4.19 % of the total participants identified as "Hispanic or Latino", and 10.31 % of the total participants did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately. *(Table 17B)*

Correspondingly, in FY2008 there were 1,873 intramural clinical research protocols, including Phase III and other clinical studies, of which 1,664 protocols reported human subject participation. *(Table 9A)* Approximately 2.8 million participants were enrolled in intramural research protocols of which 42.82% were women, 55.93% were men and 1.25% did not provide sex identification. *(Table 18A)*

In FY 2008, approximately 2.8 million participants were reported in all intramural research including Phase III clinical trials, and other clinical studies. Of the 413 intramural research protocols that report data following the former OMB standards, minority representation was highest for Blacks (not-Hispanic) at 30.34% and lowest for American Indian /Alaska Natives at 0.15%. Asian Pacific Islanders represented 3.38%, Hispanics 4.0%; and Whites (not Hispanic) 60.73% of the intramural research study population. The categories *Hawaiian Pacific Islanders* and *More Than One Race* were not designations with the former OMB standards. *(Table 16C)*

For the 1,251 intramural clinical research studies that reported data following the current OMB standards in FY 2008, the largest racial minority group was Asians at 9.8 % and the smallest racial minority group was Hawaiian Pacific Islanders at 0.2%. Blacks represented 9.4%, American Indian /Alaska Natives 0.81% and Whites 67.92% of participants in all intramural clinical research. Approximately 0.61% of participants reported *More Than One Race* as their racial category. In addition, 11.30 % did not identify a race category. Of the 1,251 intramural research protocols following the current OMB standards designating an ethnicity in FY2008, 85.30 % of total participants identified as "Not Hispanic", 4.417% of the total participants identified as "Hispanic or Latino", and 10.62 % of the total participants did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately. *(Table 18B)*

While the number of participants specifically in Phase III intramural clinical research protocols significantly decreased (3.5X) in FY2007 and 2.8X) in FY2008), there was no substantive change in the proportions of women and men (43.4%F and 55.4% M in FY2007 and 42.8%F and 55.9%M in FY2008) *(Tables 17A and Table 18A)*

NIH Defined Phase III Intramural Clinical Research: FY 2007 and FY 2008

In FY 2007 there were 38 intramural Phase III clinical research protocols, of which 36 protocols reported human subject participation. Of these, 88.8%, of the total number of protocols are domestic and 11.1% of the total number of protocols is foreign. *(Table 13A)* A total of 43,472 participants were enrolled in intramural Phase III research protocols of which 77.1 are domestic participants and 22.9% are foreign participants *(Table 13B)* Of the 43,472 participants, 52.8% were women, 47.2% were men and 0% did not provide sex identification. *(Table 19A)* Further, 27.3% of total participants in Phase III intramural clinical research protocols were reported as minorities following the current OMB categories for race and ethnicity. *(Table 13C)*

Correspondingly, in FY 2008 there were 39 intramural Phase III clinical research protocols, of which 37 protocols reported human subject participation. Of these, 89.1% of the total number of protocols is domestic and 10.8% of the total number of protocols is foreign. *(Table 13A)* A total of 16,544 participants were enrolled in intramural Phase III research protocols of which 36.7% of the total enrollment is

domestic participants and 63.2% are foreign participants. *(Table 15B)* Of the 16,544 participants, 69.71% were women, 28.92% were men and 1.37% did not provide sex identification. Further, 56.67% of total participants in Phase III clinical research protocols were reported as minorities following the current OMB categories for race and ethnicity. *(Table 20A)*

While the number of participants specifically in Phase III intramural clinical research protocols significantly decreased (43,472 in FY2007 and 16,544 in FY2008), there was a substantial increase in the proportions of women (52.8%F and 47.2%M in FY2007 and 69.7%F and 28.9%M in FY2008). *(Tables 19A and Table 20A)*

Appendix D: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research (excerpt)

TREND REPORT ON NIH AGGREGATE POPULATION DATA: FY 1995 – FY 2008

Trend data vary over time because the data for each year represent the net total of data resulting from: (1) studies continuing from the prior year; (2) the addition of new studies reported; and (3) the subtraction of studies that are no longer reported.

Table 2A is a fourteen year summary report showing a steady increase in the number of protocols and enrollment. The number of protocols with enrollment increased from 3,188 in FY1995 to 11,045 in FY2008 – a 3.5 fold increase. Reported enrollment increased from approximately 1.0 million (FY1995) to 15.4 million (FY2008) – a 15.1 fold increase; minority enrollment increased from approximately 0.4 million (FY1995) to 4.3 million (FY2008) – an 11.7 fold increase in minority representation in NIH clinical research. *(Table 2A)* The total number of protocols reported with enrollment data has increased such that, since FY2003 the number is in excess of 10,000 protocols per year. *(Table 2B)*

With the deployment of an updated population tracking system in 2002 and the OMB requirement to report data using the current format, NIH was able to report domestic and foreign data in a better way. Thus, trend data are available for domestic and foreign protocols and participation beginning in FY2002. Domestic enrollment increased from 10.2 million (FY2002) to 14.1 million (FY2008) – a 1.4 fold increase. Foreign enrollment increased from 0.9 million (FY2002) to 1.3 million (FY2008) – a 1.4 fold increase. *(Table 2A)* Overall, the total enrollment has increased with domestic participation ranging between 75.9-92.7% and foreign participation ranging between 7.3-24.1%. In FY2008, domestic and foreign enrollment was 91.7% and 8.3% respectively. *(Table 2B)*

Table 1 is a summary report of all extramural and intramural clinical research by sex/gender and minority representation following the old and new data formats for domestic and foreign studies. The report demonstrates that female participation in all extramural and intramural research generally ranged between 51.7% and 63.9%, male participation in all extramural and intramural research ranged between 34.0% and 45.0%. *(Table 1A)* Overall minority participation in all extramural and intramural clinical research ranged between 28.6% and 43.1%. *(Tables 1B-1D/Table 1E)* provides a comparison of domestic and foreign participation between FY2002 and FY2008. The vast majority of protocols are domestic (~94%-96%) of the total clinical research protocols. While the number of foreign protocols has increased, they incorporate only about 4%-6% of the total clinical research protocols with enrollment. *(Table 1F)* shows domestic and foreign enrollment for the seven-year period. Domestic minority enrollment varied between 24.1% and 28.9% of total domestic participation, while foreign minority enrollment varied between 67.7% and 90.9% of total foreign participation.

Table 4 is a summary of NIH-funded Phase III extramural and intramural clinical research by sex/gender and minority enrollment following the old and new data reporting formats for domestic and foreign studies. This table demonstrates that female participation in NIH-funded Phase III extramural and intramural clinical research generally ranged between 54.1% and 74.8% and male participation in NIH-funded Phase III extramural and intramural clinical research ranged between 24.3% and 44.6%. *(Table 4A)* Overall minority participation in NIH-funded Phase III extramural and intramural clinical research ranged from 26.9% to 41.4%. *(Tables 4B-D/ Table 4E)* provides a comparison of domestic and foreign participation between FY2002 and FY2008. The vast majority of protocols are domestic, ranging from 75.5% and 95.8% of the total clinical research protocols. While the number of foreign protocols has decreased, they incorporate only about 4.2%-9.6% of the total clinical research protocols with enrollment in the last seven years. *Table 4F* shows domestic and foreign enrollment for the seven-year period. Domestic minority enrollment varied between 20.2% and 25.4% of total domestic participation, while foreign minority enrollment in NIH-funded Phase III clinical research varied between 48.4% and 96.2% of total foreign participation. In comparing both domestic and foreign Phase III enrollment over the seven

year period shows that the small percentage of foreign protocols in FY2008 account for a significant proportion of the total foreign enrollment.

Tables 22-25 summarize domestic and foreign participation for NIH funded clinical research and NIH-funded Phase III clinical research. For extramural and intramural clinical research, domestic participants enrolled in domestic protocols, female participation ranged between 58.1% and 67.3% while male participation ranged between 30.2 and 39.5% *(Table 22.1)* For NIH-funded Phase III extramural and intramural clinical research, domestic participants enrolled in domestic protocols, female participation ranged between 53.3 and 64.6% while male participation ranged between 34.4 and 44.8% *(Table 23.1)* For all extramural and intramural clinical research, foreign participants enrolled in foreign protocols, female participation varied from 39.2% to 59.5% while male participation varied from 39.3% to 60.4% *(Table 24.1)* For NIH-funded Phase III extramural and intramural clinical research, foreign participants enrolled in foreign protocols, female participation varied from 47.4% to 59.2% while male participation varied from 40.4% to 52.5%. *(Table 25.1)*

Appendix E: Research Training and Graduate Medical Education Data

National Research Service Award (NRSA) and National Library of Medicine (NLM) Research Training Programs

Ph.D.s Awarded to NIH Trainees and Fellows		
Field of Study	FY 2007	FY 2008
Life Sciences	**2,192**	**2,369**
Biological/Biomedical Sciences	*1,943*	*2,120*
Biochemistry	188	218
Biomedical Sciences	68	72
Biophysics	64	49
Biotechnology	4	2
Bacteriology	8	4
Plant Genetics	5	7
Botany/Plant Biology	6	4
Anatomy	2	2
Bioinformatics	14	25
Biometrics & Biostatistics	25	19
Cell/Cellular Biology and Histology	131	133
Cancer Biology	43	121
Ecology	15	1
Developmental Biology/Embryology	77	69
Endocrinology	5	6
Entomology	2	2
Immunology	160	183
Molecular Biology	203	202
Microbiology	150	161

Neuroscience	327	359
Nutritional Sciences	24	19
Parasitology	6	9
Toxicology	41	46
Genetics, Human & Animal	137	147
Pathology, Human & Animal	21	37
Pharmacology, Human & Animal	96	100
Physiology, Human & Animal	64	59
Zoology, Other	1	3
Biology/Biological Sciences, General	37	28
Biology/Biomedical Sciences, Other	15	14
Health Sciences	*238*	*240*
Speech-Language Pathology & Audiology	9	12
Environmental Health	4	10
Environmental Toxicology	2	7
Health Systems/Service Administration	5	3
Public Health	39	35
Epidemiology	60	65
Kinesiology/Exercise Sciences	8	13
Nursing Science	56	60
Rehabilitation/Therapeutic Services	4	2
Veterinary Medicine	4	4
Health Sciences, General	4	3
Health Sciences, Other	22	11
Agricultural Sciences/Natural Resources	*11*	*9*
Agricultural Economics	1	1
Agricultural Science, Other	1	0
Plant Sciences, Other	0	2

Appendix E: Research Training and Graduate Medical Education Data

Environmental Science	0	3
Forest/Resources Management	1	
Social Sciences	**300**	**288**
Psychology	*235*	*224*
Clinical	81	96
Cognitive & Psycholinguistics	28	16
Counseling	2	6
Developmental & Child	24	26
Human Development & Family Studies	6	5
Experimental	14	10
Educational	2	
Industrial & Organizational	1	1
Personality	10	1
Physiological/Psychobiology	26	14
Psychometrics & Quantitative	7	0
School	1	2
Social	19	24
Psychology, General	9	12
Psychology, Other	7	10
Social Sciences	*65*	*64*
Anthropology	13	5
Demography/Population Studies	3	6
Economics	8	14
Public Policy Analysis	5	7
Sociology	23	20
Social Sciences, Other	5	0
Physical Sciences	**115**	**139**
Chemistry	*67*	*85*

Analytical	15	12
Inorganic	5	5
Organic	24	31
Medicinal/Pharmaceutical	1	0
Physical	6	10
Polymer	1	1
Theoretical	2	4
Chemistry, General	3	7
Chemistry, Other	10	15
Computer Sciences	*11*	*11*
Computer Science	10	8
Computer & Information Sciences, Other	1	2
Geological & Earth Sciences	*1*	
Geology	1	
Mathematics	*12*	*12*
Applied Mathematics	1	4
Geometry/Geometric Analysis	3	0
Statistics	5	6
Mathematics/Statistics, General	1	
Mathematics/Statistics, Other	0	1
Ocean/Marine Sciences	*2*	*0*
Marine Sciences	1	0
Oceanography, Chemical and Physical	1	0
Physics	*23*	*31*
Optics/Phototonics	1	1
Polymer Physics	1	0
Condensed Matter/Low Temperature	2	1
Physics, General	1	1

Appendix E: Research Training and Graduate Medical Education Data

Physics, Other	3	4
Engineering	**143**	**174**
Aerospace, Aeronautical & Astronautical	2	1
Bioengineering & Biomedical	99	130
Chemical	27	30
Computer	0	1
Electrical, Electronics and Communications	7	6
Environmental Health Engineering	3	1
Industrial & Manufacturing	1	0
Materials Science	1	
Mechanical	3	2
Education	**18**	**13**
Humanities	**7**	**3**
Other Fields	**26**	**17**
TOTAL	2,801	3,003
Note: Detailed field data are provided only for broad fields with ≥ 100 Ph.D. recipients		
Sources: NIH IMPAC II and the Doctorate Records File.		

Demographic Characteristics* of NRSA Participants		
Gender	FY 2007	FY 2008
Female	51.5%	51.5%
Male	45.8%	45.9%
Unreported	2.6%	2.6%
Race/Ethnicity		
White	67.2%	66.0%
Asian	15.0%	14.9%
Hispanic	6.7%	7.0%
African American	8.3%	7.6%
Native American	1.0%	1.0%
Pacific Islander	0.7%	0.7%
Unreported	5.9%	7.9%

Sources: NIH IMPAC II

*Reporting personal information such as sex, race, and ethnicity is voluntary.

Appendix E: Research Training and Graduate Medical Education Data

Graduate Medical Education: NIH-Sponsored, ACGME-Accredited, Residency and Subspecialty Training Programs

Successfully Completed Residency and Subspecialty Training By Academic Year		
NIH Clinical Center Program Specialty	Successfully Completed	
	2007/2008	2008/2009
Allergy and Immunology	4	3
Medical Genetics	4	1
Medical Biochemical Genetics	0	2
Critical Care Medicine	4	3
Endocrinology, Diabetes, and Metabolism	6	4
Hematology	3	4
Infectious Disease	3	4
Oncology	13	9
Rheumatology	2	4
Pathology-Anatomic and Clinical	4	3
Blood Banking/Transfusion Medicine	1	2
Cytopathology	1	1
Hematology (Pathology)	1	2
NICHD/Georgetown University Hospital Program / Pediatric Endocrinology*	2	3
Psychiatry	1	2
Total	49	47

*Cosponsored by NICHD and Georgetown University Hospital
Source: AAMC GME Track Database

Appendix F: Report of the Advisory Committee on Research on Women's Health, FYs 2007-2008 (excerpt)

Link to on-line version of full report can be found at http://orwh.od.nih.gov/pubs/07-08/IC/Report/Book_FINAL508.pdf

Preface

The Advisory Committee on Research on Women's Health (ACRWH), in concert with the Office of Research on Women's Health (ORWH) and the Coordinating Committee on Research on Women's Health (CCRWH), submits to the Director of the National Institutes of Health (NIH) this Biennial Report for fiscal years (FYs) 2007 and 2008. The report describes the comprehensive and coordinated efforts of the ORWH and the NIH Institutes, Centers (ICs), and Offices to address women's health issues through research and related activities in accordance with the NIH Revitalization Act of 1993. The information in this Biennial Report was prepared by the ORWH and by each of the NIH ICs and Offices to highlight significant research studies and other achievements and initiatives that have contributed to an increased knowledge of women's health. Using criteria supplied by the NIH Office of Budget, Management (OPAM) and the U.S. Department of Health and Human Services Office on Women's Health, and based on budget data provided by NIH ICs, this report also contains information on NIH budget allocations for women's health research during FY 2007 and FY 2008. In addition, the report contains information obtained from the NIH IC and Office data tracking the inclusion of women and minorities in NIH-funded clinical research during the same time period.

The ACRWH has reviewed the information contained herein and believes that this Biennial Report accurately reflects the breadth and depth of research and related activities through which the NIH in FY 2007 and FY 2008 has fulfilled its mandate from the U.S. Congress to address women's health issues and women's inclusion in research.

The ACRWH gratefully acknowledges the valuable contributions to this report of the CCRWH, which is made up of the directors of each of the ICs and Offices or their designated representatives. We are also grateful to the many NIH staff members who prepared and reviewed the reports of their ICs or Offices. We appreciate the work of the NIH Tracking and Evaluation Committee in preparing information on the inclusion of women and minorities in NIH-funded research and the work of the NIH OPAM staff in creating and tabulating the budgetary data published in this report.

Finally, the ACRWH wishes to acknowledge the work of ORWH staff. This Biennial Report highlights the achievements of the ORWH in fulfilling all aspects of its core mission to stimulate, support, and enhance research related to diseases and conditions that affect women, ensuring the appropriate representation of women in NIH research, supporting the advancement of women in biomedical careers, and building programs to ensure the development of a cadre of researchers, both women and men, in the field of interdisciplinary women's health research.

(For a full listing of ACRWH members for FY 2009, please see pages iv–vi.)

Introduction to the Biennial Report

As directed in the National Institutes of Health (NIH) Revitalization Act of 1993,[1] the Advisory Committee on Research on Women's Health (ACRWH) submits to the NIH Director a report describing the activities of the Committee and its findings related to the mandates and funding for women's health. This report includes coordinated efforts of the NIH Institutes, Centers (ICs), and Offices to address women's health issues through research and related activities. As the 20th anniversary of the establishment of the Office of Research on Women's Health (ORWH) approaches, this FY 2007–2008 Biennial Report bears witness to the phenomenal growth in women's health research and related programs that has occurred since the formation of the Office in 1990. This report reflects major FY 2007–2008 ORWH research programs, initiatives, and activities, as well as highlights that were reported through the Coordinating Committee on Research on Women's Health (CCRWH) from the NIH ICs and Offices. This report is not a comprehensive listing of all NIH research on women's health, which would necessarily be encyclopedic. However, the report does serve to summarize, under a single cover, examples of the wealth of NIH advances in women's health research. This Biennial Report also provides information on and analysis of support for women's health research and related activities. During FY 2007–2008, NIH spent approximately $[illegible] billion per year on research specifically related to women's health and approximately $[illegible] billion on research relevant to both women and men.

The Biennial Report is divided into two major parts. Part One is based on ORWH programs and describes ORWH scientific, interdisciplinary, research career development, and research dissemination and outreach programs. Data are also reported on the inclusion of women and minorities in NIH-funded clinical research as provided from the Office of Extramural Research. Many ORWH programs reflect the Office's roles in coordinating trans-NIH activities. Most ORWH programs are conducted in collaboration with NIH ICs and Offices. Other ORWH activities are conducted in collaboration with Federal agencies and/or with public and private partners. Part Two of the Biennial Report provides the individual reports on women's health research from 20 NIH Institutes, 4 Centers, and 7 Offices, which include highlights of some of their most promising research programs.

Office of Research on Women's Health

Information about ORWH programs is organized into six sections covering the following areas: ORWH Research; ORWH Interdisciplinary Research and Career Development Programs; ORWH Biomedical Career Development Activities; ORWH Research Dissemination and Outreach; Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research; and NIH Budget for Women's Health Research.

Section 1 describes FY 2007–2008 NIH women's health research priorities, developed in coordination with the CCRWH and reviewed by the ACRWH. It also provides a table of ORWH-funded projects grouped by diseases and conditions. It also provides examples of special ORWH research initiatives in FY 2007–2008 and highlights of ORWH-cofunded research projects and research workshops and conferences. A strategic planning effort, begun in 2008, is described in Section 1. The effort, which will update the 1999 *Agenda for Research on Women's Health for the 21st Century*, is currently ongoing. It is anticipated that the updated research agenda will be completed in time for the 20th anniversary of the founding of ORWH in September 2010.

The Agenda for Research on Women's Health for the 21st Century recognized that women's health research is an inherently broad interdisciplinary field of endeavor, encompassing a full range of science. Since 1999, ORWH has been working to provide institutional support for interdisciplinary research and interdisciplinary research career development. Section 2 highlights major ORWH efforts to catalyze interdisciplinary women's health research and career development through two programs.

[1] The NIH Revitalization Act of 1993 [illegible], codified at [illegible] [illegible].

the Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health, and the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Institutional Mentored Career Development Program. Section II also describes ORWH efforts to catalyze NIH interdisciplinary research and collaborations to advance understanding of a specific multisystem condition predominantly affecting women, namely chronic fatigue syndrome.

Since its inception in 1990, the mandate of ORWH has included women's career development and the development of women's health researchers. The BIRCWH program is a major example of a highly successful mentored career development program that was developed and implemented by ORWH in 2000. Section III provides information on a number of other programs through which ORWH works to promote women's biomedical career development and the development of careers in research on women's health and sex/gender factors. Section III reports on the collaborative efforts of ORWH and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) in supporting the Women's Reproductive Health Research Career Development program, and on the ORWH-facilitated trans-NIH Research and Biomedical and Behavioral Careers Research Supplement Program.

Section III describes the activities of the NIH Director's Working Group on Women in Biomedical Careers to provide an NIH response to the challenges to federal agencies posed in the 2007 National Academies of Sciences report *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*. Section III also highlights FY 2007–2008 ORWH-NIH Intramural Women's Health Research programs, ranging from a summer research program for high school students interested in science to negotiation skills for tenure-track women scientists. The section ends with a summary of a wide range of other ORWH activities to promote the career development of women, some of which involve partnering with professional societies.

Section IV on research dissemination and outreach provides information on new ORWH Internet-based health information initiatives, including a collaborative effort with the NIH National Library of Medicine to create an online resource for information on women's health research, a Web-based course co-sponsored with the Food and Drug Administration (FDA) on *How Sex and Gender in Human Health* and a multimedia approach to communicate advances being made from past and current women's health research. ORWH strives to ensure that the information generated from the NIH investment in research on women's health informs future research efforts and improves women's health care. Thus, outreach to the largest possible population of clinicians and researchers, women, healthcare providers, and others interested in women's health is a very important part of its mandate. Section IV describes ORWH outreach activities, including the Women's Health Seminar series and the Vulvodynia Awareness campaign.

Section V details NIH efforts to monitor the inclusion of women and minorities in NIH-funded clinical research, including data by FY as well as NIH aggregate figures. Section VI provides information on NIH expenditures on women's health research, including a breakdown of expenditures by disease categories and other relevant categories of interest (e.g., aging research).

NIH IC Support for Research on Women's Health

Part Two of the Biennial Report is composed of individual reports from each of 20 NIH Institutes, 4 Centers, and 7 offices located within the Office of the Director, NIH. These IC and Office reports summarize their major initiatives and activities and provide highlights of their funded research related to women's health and sex/gender research, consistent with their specific missions.

You are invited to read this in-depth report to become acquainted with the tremendous advances in women's health research that have taken place during this 2-year period and to appreciate the promise for even greater advances in the future, not just for women's health but also for men's health and for careers in women's health research for both men and women.

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health

Office of Research on Women's Health (ORWH)

INTRODUCTION TO ORWH PROGRAMS

In 1983, the Assistant Secretary for Health, Dr. Edward N. Brandt, established the U.S. Public Health Service Task Force on Women's Health Issues, in recognition of the paucity of data related to women's health. The Task Force produced a 1985 report, *Women's Health: Report of the Public Health Service Task Force on Women's Health Issues, Volume I*.[1] The report delineated a series of criteria for differentiating a health problem, condition, or disease as a woman's issue. The criteria included the following:

- Diseases or conditions unique to women or some subgroup of women;
- Diseases or conditions more prevalent in women or some subgroup of women;
- Diseases or conditions more serious in women or some subgroup of women;
- Diseases or conditions for which risk factors are different for women or some subgroup of women; or
- Diseases or conditions for which interventions are different in women or some subgroup of women.

The report also recommended that "biomedical and behavioral research should be expanded to ensure emphasis on conditions and diseases unique to, or more prevalent in, women in all age groups."

Following the issuance of the Task Force report, the National Institutes of Health (NIH) established a policy for the inclusion of women in clinical research. This policy, which urged the inclusion of women, was first published in the *NIH Guide to Grants and Contracts* in 1987.[2] Later that year, minority scientists and other researchers at NIH recognized the need to address the inclusion of minority populations. As a result, a subsequent version of the NIH Guide published for the first time a policy encouraging the inclusion of minorities in clinical studies.[3]

In 1990, the Congressional Caucus for Women's Issues requested that the General Accounting Office (GAO) (now known as the Government Accountability Office) conduct an investigation into the implementation of the guidelines for the inclusion of women by NIH. This report, included in congressional testimony, indicated that the implementation of the policy for the inclusion of women was slow and not well communicated, that gender analysis was not being performed routinely, and that the impact of this policy could not be determined.[4] The GAO testimony also indicated that there were differences in the implementation of the policy recommending the inclusion of minorities, and that not all Institutes and Centers (ICs) included adherence to these policies into scientific merit review. GAO findings concerning the lack of consistent implementation of policies for inclusion of women in NIH clinical trials led NIH to establish the ORWH within the Office of the

[1] U.S. Public Health Service. Women's Health: Report of the Public Health Service Task Force on Women's Health Issues. [illegible]

[2] Division of Research Resources. Inclusion of women in study populations. *NIH Guide for Grants and Contracts*. [illegible]

[3] Division of Research Resources. Inclusion of minorities in study populations. *NIH Guide for Grants and Contracts*. [illegible]

[4] [illegible] (GAO/T-HRD-90-38). [illegible] Washington, DC: [illegible]

NIH Director in September 1990. Since its establishment, ORWH has served as the focal point for women's health research at NIH. The responsibilities of the Director, ORWH, include the following:

(1) Advises the NIH Director and staff on matters relating to research on women's health;

(2) Strengthens and enhances research related to diseases, disorders, and conditions that affect women;

(3) Ensures that research conducted and supported by NIH adequately addresses issues regarding women's health;

(4) Ensures that women are appropriately represented in biomedical and biobehavioral research studies supported by NIH;

(5) Develops opportunities for and supports recruitment, retention, reentry, and advancement of women in biomedical careers; and

(6) Supports research on women's health issues. ORWH works in partnership with the NIH Institutes and Centers to ensure that women's health research is part of the scientific framework at NIH and throughout the scientific community.

ORWH was established in statute in the NIH Revitalization Act of 1993.[6] An Advisory Committee on Research on Women's Health (ACRWH), composed of non-Federal members, was also statutorily mandated in the Revitalization Act as a mechanism for eliciting advice and recommendations on priority issues affecting women's health research. This Committee provides leadership to ORWH by advising the ORWH Director on appropriate research activities in women's health. ACRWH members are chosen from among health practitioners, advocates, research scientists, educators, and other professionals. Committee members are actively involved in reviewing and advising on matters related to research priorities, the women's health research portfolio for NIH, career development, inclusion of women and minorities in NIH-funded clinical research, and other ORWH or NIH programs related to women's health.

ORWH also benefits from the advice of a Coordinating Committee on Research on Women's Health (CCRWH). The CCRWH was also established in statute in the 1993 NIH Revitalization Act and is composed of Institute and Center Directors or their designees as a direct liaison for ORWH with NIH ICs. Both the ACRWH and the CCRWH provide valuable guidance, collaboration, and support for activities of ORWH in women's health research, career programs, and outreach efforts.

ORWH programs and efforts have expanded in breadth and depth over the years. The research funded or cofunded by ORWH is based on collaborative efforts with the ICs and supports peer-reviewed, science-driven initiatives. These collaborations are benefiting the health of all Americans across the lifespan, men as well as women, and all racial and ethnic groups.

[6] The NIH Revitalization Act of 1993 [illegible]

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