2 SUMMARY OF RESEARCH ACTIVITES BY DISEASE CATEGORY

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Volume II Contents

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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.
[6] American Cancer Society. Facts and Figures 2009.
[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.

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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]

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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.
[37] For more information, see http://www.cdc.gov/nchs/fastats/deaths.htm.
[38] CDC Cases of HIV Infection and AIDS in the United States and Dependent Areas, by Race/Ethnicity, 2003—2007, Table 4. See http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2009supp_vol14no2/table4.htm
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[40] For information about funding for research through the NIH Evolution of Infectious Diseases Program, see http://grants.nih.gov/grants/guide/pa-files/PA-07-130.html. See also Rosenthal JP, Jessup CM. *Trans Am Clin Climatol Assoc* 2009;120:129-41. PMID: 19768170. PMCID: PMC2744516.
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[42] For information about NIH funding for research on antimicrobial and prebiotic activity of oligosaccharides, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-004.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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[51] For more information, see http://www3.niaid.nih.gov/topics/tuberculosis/Research/NIAIDsRole.htm.
[52] For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/research/.
[53] For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/prevention/research/Microbicides/research.htm.
[54] For more information, see http://www.prepwatch.org/.
[55] For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/test_treat.htm.
[56] For more information, see http://statepiaps.jhsph.edu/naaccord/.
[57] For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-09-017.html.
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[60] For more information, see http://www.oar.nih.gov/strategicplan/fy2010/pdf/Chapter5.pdf.
[61] For more information, see http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm.
[62] For more information, see http://www.vacohort.org/.
[63] For more information, see http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html.
[64] For more information, see http://www3.niaid.nih.gov/topics/Flu/understandingFlu/2009h1n1.htm.
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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)*
- *Women's Health in the U.S.: Research on Health Issues Affecting Women (2004)*

National Center for Complementary and Alternative Medicine (NCCAM)

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

Trans-NIH Plans

- *NIH Autoimmune Diseases Coordinating Committee: Autoimmune Diseases Research Plan*
  (CSR, FIC, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, **NIAID**, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, ORD, ORWH)
- *NIH Action Plan for Transplantation Research (2007)*
  (NCI, NHLBI, NIA, NIAAA, **NIAID**, NIAMS, NIBIB, NIDA, NIDCR, NIDDK, NIMH, NINDS)
- *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*
  (CC, CSR, NCCAM , NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, **NIDDK**, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)
- 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)

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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]

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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.
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→ 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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[104] Ibid.
[105] For more information, see http://www.nhlbi.nih.gov/health/dci/index.html.
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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.

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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.

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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.

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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.
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→ 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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Teitelbaum SL, et al. *Environ Res* 2008;106(2):257-69. PMID: 17976571.
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→ 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.

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→ 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.
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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 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.

→ Mahalingaiah S, et al. *Environ Health Perspect* 2008;116(2):173-8. PMID: 18288314. PMCID: PMC2235217.
Leranth C, et al. *Proc Natl Acad Sci U S A* 2008;105(37):14187-91. PMID: 18768812. PMCID: PMC2544599.
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Hunt PA, Hassold TJ. *Trends Genet* 2008;24(2):86-93. PMID: 18192063.

→ 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.

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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/rircmi
→ 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		

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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

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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			

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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

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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			

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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

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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	

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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	

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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

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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	

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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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