Summary of Research Activities by Disease Categories

Cancer

By the late 1970s, it was well known that genes from viruses could rapidly transform normal cells into cancer cells and that the viruses acquired these genes from the genomes of the animals and birds that they infected. In 1982, three separate laboratories all cloned the first human cancer-causing gene, called an "oncogene." This discovery was the result of the laborious process of testing increasingly smaller pieces of DNA from a cancer cell for the ability to cause cancer. Subsequent studies confirmed that the oncogene was a version of a gene called ras, which had been incorporated into the mouse genome from a mouse virus. The ras gene in the mouse virus had a single genetic change that caused it to induce uncontrolled growth that resulted in cancer. This elegant work confirmed what had previously been just a notion—that cancer was a disease of altered genes. This finding began the era of modern molecular cancer research and treatment[1].

Introduction

Cells are the building blocks of all living things. Normal cells multiply in an orderly way and die when no longer needed. Cancer can be described as uncontrolled growth of abnormal cells from almost any organ or tissue within the body. The process that leads to cell death is often blocked in cancer cells. Cancer cells can invade nearby tissues and spread to other parts of the body. Because it takes so many forms and occurs in so many parts of the body, cancer should be thought of not as a single disease but as a complex set of diseases that must be studied from multiple perspectives.

The National Institutes of Health's (NIH's) strategic approach to cancer research 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.

NIH also coordinates transdisciplinary translational research designed to realize a vision of personalized medicine. As this vision evolves, doctors will be able to use detailed information about an individual's tumor 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.

Several examples illustrate the types of research advances and promising new initiatives achieved by NIH scientists and grantees. For example, Gardasil®, the first vaccine to prevent cervical cancer induced by human papillomavirus (HPV), has the potential to save over 200,000 women's lives worldwide each year, including 5,000 U.S. women's lives. In another example, using whole-genome scans, the Cancer Genetic Markers of Susceptibility project has pinpointed common genetic variants associated with increased risk of breast and prostate cancers. In addition, the National Cancer Institute (NCI) and the National Institute of Environmental Health Sciences (NIEHS) have launched the Breast Cancer and Environment Research Centers to study the impact of prenatal-to-adult environmental exposures that may predispose a woman to breast cancer.

[1] For more information, see http://www.nature.com/milestones/milecancer/full/milecancer17.html

Cancer research is conducted by a number of NIH Institutes and Centers (ICs); most of the research investment is committed to NCI programs. 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 rapidly translating those findings into novel preventive and detection methods and therapies. 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).

Cancer research conducted or supported by other NIH ICs is wide ranging and often is 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 NCI-funded Comprehensive Cancer Centers. Examples of cancer research within other ICs include:

- National Institute on Aging (NIA) research on prostate and skin cancers and the biology of aging as it relates to cancer
- NIEHS research on the effects of biological, chemical, or physical agents on human health
- 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 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 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 Neurological Disorders and Stroke (NINDS) research on brain, spinal cord, and pituitary cancers
- National Institute of Nursing Research (NINR) HIV/AIDS and Oncology program
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) research on breast and reproductive cancers
- National Institute of General Medical Sciences (NIGMS) cancer-related basic biomedical research
- National Institute of Biomedical Imaging and Bioengineering (NIBIB) imaging and bioinformatics technology development in areas that are vital to cancer research
- National Institute on Drug Abuse (NIDA) research on treatments for tobacco addiction serving as cancer prevention

Burden of Illness and Related Health Statistics

Because cancer is the second leading cause of death in the United States and the economic cost of cancer in 2005 was estimated at over $200 billion (including $74 billion in direct health care costs and over $135 billion in indirect costs associated with lost productivity due to illness and premature death), cancer research is a major NIH priority[2]. Although significant progress has been made toward reducing the burden of cancer in America, cancer

[2] For more information, see http://obf.cancer.gov/financial/attachments/06Factbk.pdf

remains a leading cause of death, second only to heart disease—one of every four deaths is due to cancer[3], [4]. The American Cancer Society estimated that, in 2007, there were about 1,444,920 new diagnoses of invasive cancer and 564,830 Americans died of cancer[5]. 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% to 15 million new cases in the year 2020.

One sign of progress is that U.S. death rates for the most common cancers and for all cancers combined have decreased significantly since 1995[6]. 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. Increasing numbers of Americans are surviving cancer. NIH estimated that, on January 1, 2003, 10.5 million living Americans had a history of invasive cancer[7]. [7]These numbers are likely to increase because of the anticipated growth and aging of the U.S. population[8].

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 cancer, lung cancer, and colon cancer[9].

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 the section "Minority Health and Health Disparities" later in this chapter.

NIH Funding for Cancer Research

In FYs 2006 and 2007, NIH funding for cancer research was $5.575 billion and $5.643 billion respectively. The table at the end of this chapter indicates some of the research areas involved in this investment (see "Estimates of Funding for Various Diseases, Conditions, and Research Areas").

Summary of NIH Activities

Across NIH, cancer 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

[3] For more information, see http://www.cancer.org.

[4] For more information, see http://www.cdc.gov/nccdphp/burdenbook2004/index.htm

[5] American Cancer Society, 2005.

[6] NCI, 2006.

[7] For more information, see http://seer.cancer.gov/csr/1975_2003

[8] Edwards BK, et al. *Cancer* 2002;94:2766-92, PMID: 12173348

[9] NCI, 2006.

- 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 is also 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 to our ability to develop and apply interventions to preempt cancer's initiation and progression. NIH's plan for deciphering the causes and mechanisms of cancer includes 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 could also 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 Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatments (TARGET)** initiative identifies and validates therapeutic targets for childhood cancers beginning with acute lymphoblastic leukemia and neuroblastoma.

Genetic susceptibility to cancer and cancer risk associated with environmental exposures are also important research topics. Using powerful new technologies to scan the entire human genome, NIH is conducting genome-wide association studies to identify unsuspected genetic variants associated with cancer risk. 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 genome-wide studies 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 is also supporting a network of Breast Cancer and 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.

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. NIH is actively pursuing research on the linkages between carcinogenesis and alterations in the microenvironment induced by inflammation. Inflammation is a response to acute tissue damage, whether resulting from physical injury, infection, exposure to toxins, or other types of trauma. 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.

Another area of research focus at NIH is the interface between aging and cancer. As part of an interagency collaborative effort, eight NCI-designated Cancer Centers are conducting studies on the biology of aging and cancer and addressing questions related to cancer prevention, treatment, and survivorship in older patients. This research will help provide insights into why cancer occurs more frequently in older people, whether cancer behaves differently in older adults than in younger people, whether older patients respond differently to treatment, and how prevention and screening services should be adapted for this population.

Angiogenesis–the growth of new blood vessels–is required at a certain point for tumors to continue to grow beyond a size at which they begin to need their own blood supply. Thus, blockade of angiogenesis can prevent tumor growth. The NIH Trans-Institute Angiogenesis Research Program funds promising angiogenesis research. The program's multidisciplinary approach fosters data exchange and resource sharing among vascular biology and angiogenesis researchers from different disease disciplines. A number of new angiogenesis inhibitors are currently being developed, including several in late-stage clinical trials.

Systems biology and systems genetics are also 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 are often 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.

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.

A major step forward in our efforts to prevent cancer has been the development of vaccines that target 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–is now 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.

Another area of focus in cancer prevention is cancer's relationship with diet and obesity. In its 2006-2007 Annual Report, the President's Cancer Panel cites evidence that as many as one-third of the nearly 600,000 yearly cancer deaths in the United States can be attributed to unhealthy diets and obesity. 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. The TREC research 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 area of diet, physical activity, and weight and is integrated with the NIH Obesity Research Task Force Strategic Plan.

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 is also a trans-HHS victory, as significant research investments have been made over the last 50 years by NCI, NHLBI, NIDA, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the John E. Fogarty International Center (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 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. Over the past 23 years, more than 200,000 people have enrolled in clinical trials involving CCOP investigators and institutions. One example is the Study of Tamoxifen and Raloxifene (STAR), which compared the drug raloxifene with the drug tamoxifen in reducing invasive breast cancer in high-risk postmenopausal women. The initial results from STAR indicate that raloxifene is as effective as tamoxifen with fewer side effects. The FDA Oncology Drug Advisory Committee has recommended approval of raloxifene for breast cancer prevention.

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.

One NIH effort in the area of early detection is the National Lung Screening Trial (NLST), which is comparing two ways of detecting lung cancer–spiral computed tomography (CT) scans and standard chest X-rays. This study aims to answer the important question whether deaths from lung cancer can be reduced through the use of CT screening. Research has shown that spiral CT is capable of detecting not only smaller lung abnormalities, but also more lung cancers than chest x-ray. However, most of the lung abnormalities seen on screening spiral CTs are not cancer. Moreover, it is not known if finding these lung abnormalities will actually benefit people by lowering deaths from lung cancer. NLST is designed to scientifically answer the question of which screening test will better reduce lung cancer deaths and make meaningful recommendations for public policy.

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 to bring a collaborative approach to the discovery, development, and validation of early-detection biomarkers for clinical application. Another NIH program, the Strategic Partnering to Evaluate Cancer Signatures program, 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 Web site 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 its Clinical Proteomic Technologies Initiative for Cancer. 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 the infrastructure needed to systematically advance our understanding of protein biology in cancer and accelerate basic science research and the development of clinical applications.

---

[10] Thun MJ, Jemal A. Tobacco Control 2006;15:345-7, PMID: 16998161

The first product of an NIH-funded research project to integrate new technologies into a reliable clinical protocol to improve oral cancer detection has reached the market. Researchers report success using a customized optical device that allows dentists to visualize in a completely new way whether a patient might have a developing oral cancer. Deviations from the natural fluorescence of healthy tissue may indicate the presence of developing tumor cells. Health care providers can shine a light onto a suspicious sore in the mouth, look through an attached eyepiece, and check for changes in color. The instrument is an effective aid in screening and can guide surgeons when removing tissue for biopsies.

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 our ability to identify 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), safely shortens the timeline for moving anticancer drugs from the laboratory to the clinic by combining NIH expertise in drug development with state-of-the art research facilities. This program takes advantage of new FDA guidelines that allow human trials, referred to as “Phase 0” or “Early Phase I” trials, to proceed before traditional, expensive, time-consuming drug development steps have occurred. The first Phase 0 study has been successfully completed, demonstrating that this new approach can reduce the number of patients required for an early clinical study and shorten the time necessary to gather critical drug development information.

Another NIH 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.

In addition, NIH’s Radiation Research Program (RRP) evaluates the effectiveness of radiation research conducted by grantees. The RRP coordinates its activities with other radiation research programs at NIH, other Federal agencies, and national and international research organizations. Currently, major clinical trials are evaluating radiation therapy dose escalation, as well as novel combinations of chemotherapy with concomitant boost radiation therapy, in non-small cell lung cancer (NSCLC).

Marshalling the exquisite specificity of the immune system to selectively target cancer cells without harming normal cells is another focus of cancer treatment research at NIH. The Cancer Vaccine and Immunotherapy Program is evaluating therapeutic cancer vaccines aimed at antigens that are unique to or overexpressed by cancer cells. Other approaches under evaluation include immunotherapy with T lymphocytes that specifically kill cancer cells, monoclonal antibodies and immunotoxins that target cancer cells, and the use of cytokines that boost the body’s ability to fight cancer. These a pproaches may be used in combination with conventional treatments for cancer, such as chemotherapy and radiotherapy.

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 towards clinical application, and bring novel therapeutic options to the management of human cancers. As part of this effort, COP has established a multi-center collaborative network of extramural comparative oncology programs that have completed three clinical trials this year and plans to initiate five additional trials.

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, life styles, 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 ensuring the best outcomes for all overcoming health disparities in cancer incidence and outcomes is described in a later section of this chapter (see "Minority Health and Health Disparities").

NIH is currently engaged in making cancer a working model for quality-of-care research and the translation of the findings of this research 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, the Centers for Medicare and Medicaid Services, and the Department of Veterans Affairs; (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; (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, the Prostate Cancer Outcomes Study, and studies utilizing the SEER-Medicare Database. 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.

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. NIH cancer survivorship research 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 to health care providers. The Cancer Control P.L.A.N.E.T. Web 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 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 the cancer 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 for accessing products and guidelines for planning and evaluation.

Infrastructure for Research

NIH places a high priority on technology development (see the section "Technology Development" in this chapter) 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 will be increasingly 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 that has been launched 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. NIH is committed to bringing caBIG™ into an enterprise model that can be extended and sustained across a broader community.

Another initiative, the NCI Alliance for Nanotechnology in Cancer, is a comprehensive endeavor that involves both the public and the private sectors and 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.

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.

Personalized Medicine

Advances in these critical aspects 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 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 have already yielded progress toward reaching 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.

Notable Examples of NIH Activity

Key for Bulleted Items:

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported through a congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = Concerns progress tracked under the **G**overnment **P**erformance and **R**esults **A**ct

Initiatives and Major Programs

Clinical Proteomic Technologies Initiative for Cancer: 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 research to clinical application through its Clinical Proteomic Technologies Initiative for Cancer. 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 the infrastructure needed to systematically advance our understanding of protein biology in cancer and accelerate discovery research and clinical applications.

- For more information, see http://proteomics.cancer.gov
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*.
- (E/I) (NCI)

NCI Alliance for Nanotechnology in Cancer: The NCI Alliance for Nanotechnology in Cancer is a comprehensive, systematized initiative that encompasses the public and private sectors and is designed to accelerate the application of the best capabilities of nanotechnology to cancer. The program supports research on novel nanodevices that may 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 malignant cells. Nanotechnology is likely to change the very foundations of cancer diagnosis, treatment, and prevention.

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

Cancer Imaging Program (CIP): The CIP's mission is to promote and support cancer-related basic, translational, and clinical research in the imaging sciences. CIP initiatives include (1) development and delivery of image-dependent interventions for cancer and pre-cancer; (2) development of standardized models for the design of clinical trials using imaging; (3) development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput screening; and (4) development of imaging methods to detect, treat, and monitor response to therapy.

- For more information, see http://imaging.cancer.gov
- This example also appears in Chapter 3: *Technology Development*
- (I/E) (NCI)

Clinical Trials Networks: The Clinical Trials Networks are part of the infrastructure that allows patients and community physicians access to national studies, facilitating the ability to put successful regimens into practice:

- The Community Clinical Oncology Program (CCOP) is a network for conducting cancer prevention and treatment clinical trials. In 23 years of CCOPs, more than 200,000 people have enrolled in treatment and prevention trials. An example is the Study of Tamoxifen and Raloxifene (STAR), which compares the effectiveness of these two drugs for reducing the incidence of breast cancer in postmenopausal women at increased risk of the disease. Initial results indicate that raloxifene is as effective as tamoxifen with fewer side effects. (For more information, visit http://www.cancer.gov/STAR and http://dcp.cancer.gov/programs-resources/programs/ccop.)
- Cooperative Group Trials consist of researchers, Cancer Centers, and community doctors who investigate new cancer treatment, prevention, early detection, quality of life, and rehabilitation. They involve more than 1,700 institutions, thousands of individual investigators, and more than 22,000 patients each year. These trials are testing therapies that demonstrate improvement to overall patient survival. For example, the Bevacizumab with Platin-Based Chemotherapy study showed that when the monoclonal antibody bevacizumab is added to a paclitaxel-carboplatin chemotherapy regimen for patients with NSCLC, their overall survival, progression-free survival, and response rates significantly increased. (For more information, visit http://ctep.cancer.gov.)
- The NCI Community Cancer Centers Program (NCCCP) is a 3-year pilot program to test the concept of a national network of community cancer centers to alleviate inadequate care delivery. NCCCP will develop and evaluate programs on community-based cancer care and identify ways to facilitate their broader engagement in cancer research. (For more information, visit http://ncccp.cancer.gov.)

    - This example also appears in Chapter 3: *Clinical and Translational Research*.
    - (E) (NCI)

Community Networks Program (CNP): The CNP aims to reduce and eliminate cancer disparities among racial minorities through community-based research, education, and training. The goals of the program are to significantly improve access to and utilization of beneficial cancer interventions in communities with cancer disparities. A total of 25 projects across the United States and in American Samoa were launched in May 2005 to address cancer disparities among African Americans, American Indians/Alaska Natives, Hawaiian Natives and other Pacific Islanders, Asians, Hispanics/Latinos, and rural underserved populations. Ten grantees work in local areas, 10 in regional areas, and 5 in national programs. Visit: http://crchd.cancer.gov/cnp/overview.html.

- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCI)

Genome-Wide Association Studies of Cancer Risk: Beginning with the Cancer Genetic Markers of Susceptibility (CGEMS) initiative for breast and prostate cancer, NIH has capitalized on its long-term investment in intramural and extramural consortia by creating strategic partnerships to accelerate knowledge about the genetic and environmental components of cancer induction and progression. With powerful new technology capable of scanning the entire human genome, these efforts have recently identified unsuspected genetic variants associated with increased risk for developing cancers of the prostate, breast, and colon. Additional scans, either planned or under way, will be directed at cancers of the pancreas, bladder, lung, and other organs. The results of these genome-wide studies, together with the follow-on studies planned to narrow the search for causal gene variants, promise to provide novel clinical strategies for early detection, prevention, and therapy. To expand upon these emerging opportunities, a new Laboratory of Translational Genomics (LTG) has been established to further characterize genetic regions associated with cancer susceptibility and to identify gene-gene and gene-environment interactions. The LTG will create opportunities for collaboration and data sharing to accelerate the translation of genomic findings into clinical interventions.

- For more information, see http://cgems.cancer.gov/
- For more information, see http://epi.grants.cancer.gov/BPC3/cohorts.html
- For more information, see http://epi.grants.cancer.gov/PanScan
- For more information, see http://cgems.cancer.gov/index.asp
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*.
- (E/I) (NCI)

NCI Experimental Therapeutics Program (NExT): The NExT program safely shortens the timeline for taking anticancer drugs from the laboratory to the clinic by combining NIH's expertise in drug development with state-of-the art research facilities. The program also utilizes new FDA guidelines that allow early Phase I clinical trials to proceed before certain time-consuming and expensive drug development steps occur. The first such study passed the initial stage of clinical examination demonstrating that this new type of trial can reduce the number of patients required for an early clinical study and the time necessary to gather critical drug development information.

- For more information, see http://dctd.cancer.gov/MajorInitiatives/02NExT.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E/I) (NCI)

Systems Biology and Systems Genetics: NIH launched the Integrative Cancer Biology Program to focus on networks that can be measured, modeled, and manipulated rather than individual components. Multidisciplinary teams are critical to integrating the disciplines of biology, medicine, engineering, math, and computer science (e.g., computational biology). Equally important to our understanding of cancer is systems genetic research (systems biology and 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 Sciences* and Chapter 3: *Technology Development*.
- (E) (NCI)

The Cancer Biomedical Informatics Grid™: The Cancer Biomedical Informatics Grid™ (caBIG™) initiative has been launched to accelerate research discoveries and improve patient outcomes by linking researchers, physicians, and patients throughout the cancer community. date represents a new phase of evolution, as NIH is committed to bringing caBIG™ into an enterprise model that can be extended and sustained across a broader community.

- For more information, see http://cabig.cancer.gov
- This example also appears in Chapter 3: *Technology Development*.
- (E/I) (NCI)

The Cancer Genome Anatomy Project (CGAP): The goal of CGAP is to determine the gene expression profiles of normal, precancer, and cancer cells to improve detection, diagnosis, and treatment for the patient. The CGAP Web site makes various tools for genomic analysis available to researchers. Through worldwide collaborations, CGAP seeks to increase its scientific expertise and expand its databases for the benefit of all cancer researchers.

- For more information, see http://cgap.nci.nih.gov/
- This example also appears in Chapter 3: *Genomics*.
- (E/I) (NCI)

The Cancer Imaging Program (CIP): The mission of CIP is to promote and support cancer-related basic,

translational and clinical research in imaging sciences. CIP initiatives include: a) development and delivery of image-dependent interventions for cancer and pre-cancer; b) standardized models for the design of clinical trials using imaging; c) development of emerging imaging technologies, including nanotechnology, proteomics, and high-throughput screening; and d) development of imaging methods to detect, treat and monitor response to therapy.

- For more information, see http://imaging.cancer.gov/
- This example also appears in Chapter 3: *Technology Development*.
- (E/I) (NCI)

The NCI Alliance for Nanotechnology in Cancer: This is a comprehensive, systematized initiative encompassing the public and private sectors, designed to accelerate the application of the best capabilities of nanotechnology to cancer. The program supports research on novel nanodevices that may detect and pinpoint the location of cancer at its earliest stages, deliver anticancer drugs specifically to malignant cells, and determine in real-time if these drugs are effective in killing malignant cells. Nanotechnology will likely change the very foundations of cancer diagnosis, treatment and prevention.

- 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)

The Radiation Research Program (RRP): The RRP establishes priorities, allocates resources, and evaluates the effectiveness of radiation research and coordinates with other Federal radiation research programs. RRP has established guidelines for studying proton radiation therapy. Major trials are evaluating radiation dose escalation in NSCLC and novel combinations of chemotherapy with concomitant-boost radiation therapy in patients with NSCLC.

- Bonner JA, et al. *N Engl J Med*. 2006;354:567-78, PMID: 16467544
- Bao S, et al. *Nature*. 2006;444:756-60, PMID: 17051156
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (I) (NCI)

The Tumor Biology and Metastasis Program: The Tumor Biology and Metastasis Program supports research to delineate the molecular mechanisms and signaling pathways involved in tumor progression, cell migration and invasion, angiogenesis, lymphangiogenesis, and metastasis. Research indicates that the progression of cancer depends on the co-evolution of carcinoma cells in their immediate microenvironment. In 2006, NIH launched the Tumor Microenvironment Network (TMEN) to investigate the composition of the stroma in normal tissues. The goal of this network is to delineate the mechanisms of tumor-stromal interactions in human cancer.

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

The NCI Vaccine Program: NCI's vaccine program develops novel vaccines for cancer immunotherapy and prevention and HIV. The program encourages collaborations, identifies organizational and reagent needs for the community, and develops the optimal infrastructure for vaccine development and novel clinical trial approaches. Gardasil®, the first vaccine to prevent cervical cancer induced by HPV, is now available and can potentially save more than 5,000 U.S. women's lives each year. This FDA-approved vaccine resulted from basic research performed at NIH that produced a prototype vaccine and the observation that linked HPV and cervical cancer.

- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NCI)

Long-Term Cancer Survivors Research Initiatives: The population of cancer patients surviving more than 5 years continues to grow across life stages, from children through senior adults. These research initiatives focus on the physiological and psychosocial effects of treatment, as well as medical 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. Implications include the length and quality of survival and the ongoing burden of illness and costs.

- For more information, see http://cancercontrol.cancer.gov/bb/2006_bb.pdf#page=93
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-04-003.html
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NCI, CDC, NIA)

International Tobacco and Health Research and Capacity Building Program: Without a significant shift in worldwide smoking patterns, tobacco is projected to cause roughly 10 million deaths each year by 2025; 70 percent of this increase will occur in developing countries. To address this rising epidemic, NIH reissued the International Tobacco and Health Research and Capacity Building Program for funding in 2007. Grantees are generating a solid evidence base that can inform effective tobacco control strategies and policies. The program focuses on five critical areas: epidemiology and surveillance, susceptibility and risk for smoking uptake, behavioral and social sciences, effective interventions, and policy-related research. The program also emphasizes research on determinants of youth smoking in diverse cultural and economic settings. A central goal of this program is to strengthen capacity in tobacco research in low- and middle-income nations, which advances the science and permits greater international collaboration.

- For more information, see http://www.fic.nih.gov/programs/research_grants/tobacco/index.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (FIC, NCI, NIDA, NIDCR, ORWH)

The Program in HIV/AIDS & Cancer Virology: The mission of the Program in HIV/AIDS & Cancer Virology is to facilitate and rapidly communicate advances in the discovery, development, and delivery of antiviral and immunologic approaches for the prevention and treatment of HIV infection, AIDS-related malignancies, and cancer-associated viral diseases. This includes basic laboratory, translational, and clinical studies of disease pathogenesis, the development of novel targeted treatment approaches for cancers in HIV-infected individuals and for HIV infection itself, and drug resistance. Recent advances include a new prophylactic vaccine for HPV and promising candidates for prophylactic and therapeutic vaccines against HIV infection.

- For more information, see http://ccr.nci.nih.gov
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E/I) (NCI)

Trans-Institute Angiogenesis Research Program (TARP): TARP encourages and facilitates the study of angiogenesis, the formation of new blood vessels. A number of common disease conditions are angiogenesis dependent, including some cancers, macular degeneration, atherosclerosis, diabetic retinopathy, and many others. Cancers cannot grow beyond a certain size without new blood vessels. According to one estimate, more than 500

million people could benefit from anti- or pro-angiogenesis treatments in the coming decades. TARP funds promising angiogenesis research and provides training and workshops to communicate state-of-the-art preclinical and clinical angiogenesis research. The program's multidisciplinary approach fosters data exchange and resource sharing among vascular biology and angiogenesis researchers from different disease disciplines. A number of new angiogenesis inhibitors are currently being developed, including several in late-stage clinical trials.

- For more information, see http://www.tarp.nih.gov/funding.html
- (E) (**NCI**, NEI, NHLBI, NICHD, NIDDK, NINDS)

The Sister Study: The Sister Study is a major NIH initiative to study environmental and genetic risk factors for breast cancer in a cohort of 50,000 sisters of women who have had breast cancer. The asymptomatic women 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.

- For more information, see http://www.sisterstudy.org/English/index1.htm
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NIEHS)

Brain Tumor: The NIH Brain Tumor Progress Review Group identified many priorities for the field. Research on understanding and preventing brain tumor dispersal was one of the group's highest scientific priorities, and NIH funds a number of projects in this area, many of which were submitted in response to a Program Announcement with set-aside funds issued in 2004. 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.

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

Cancer Stem Cells: NIH is expanding its research portfolio related to the basic biology of tumor-initiating cells (i.e., stem cells) within the hematological and solid-tumor malignancies. Tumor stem cells are a minor population of cells thought to be capable of reconstituting an entire tumor. This is extremely important clinically in that these cells may be responsible for the recurrence of malignancy. Progress has been made in identifying such minority populations of tumor stem cells in both multiple myeloma and acute myelogenous leukemia. These tumor-initiating cells are resistant to standard chemotherapeutic agents but may contain "stem cell-unique" target molecules that may allow their eradication with novel small molecular therapeutics. Progress in identifying tumor "stem cells" among solid tumors has also been made in breast cancer, where the minority of "stem cells" have been separated and characterized from the majority of breast cancer cells in the tumor.

- For more information, see http://stemcells.nih.gov/index.asp
- (E/I) (NCI)

Exemplary Current Studies and Projects

Cancer and Inflammation: NIH is actively pursuing research on the relationship between alterations in the lung microenvironment caused by inflammation and carcinogenesis. Inflammation is a response to acute tissue

damage, whether resulting from physical injury, ischemic injury, infection, exposure to toxins, or other types of trauma. Current research on inflammation suggests pro-inflammatory conditions such as chronic pulmonary irritation contribute to the development of lung cancer and may be strongly correlated with the occurrence of lung cancer in nonsmokers. Ongoing studies are investigating inflammation in stomach, liver, and other cancers.

- (E/I) (NCI)

Molecular Profiling of Cancer: The underlying cause of each patient's disease is typically unique to the individual. Because each tumor has its own biological properties, molecular profiling provides advanced analysis and tools to characterize each individuals' disease or tumor so that tailored medical strategies can be given. Several notable examples include:

- The Early Detection Research Network (EDRN) brings together dozens of institutions to help detect cancer in its earliest stages. EDRN was formed to bring a collaborative approach to the discovery, development, and validation of early detection markers by accelerating the translation of biomarker information into clinical applications.
- The Strategic Partnering to Evaluate Cancer Signatures (SPECS) Program establishes strategic partnerships to bring together interdisciplinary teams to evaluate the clinical utility of molecular signatures. SPECS focuses on confirming, evaluating, and refining signatures and/or profiles derived from molecular analysis of tumors (i.e., biomarkers detection) to improve patient management and outcomes.

- For more information, see http://edrn.nci.nih.gov/
- For more information, see http://www.cancerdiagnosis.nci.nih.gov/specs/index.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E/I) (NCI)

The Cancer Genome Atlas (TCGA): TCGA is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. The goal of TCGA is to develop a free, rapidly available, publicly accessible, comprehensive catalog, or atlas, of the many genetic changes that occur in cancers, from chromosome rearrangements to DNA mutations to epigenetic changes–the chemical modifications of DNA that can turn genes on or off without altering the DNA sequence. The overarching goal of TCGA is to improve our ability to diagnose, treat, and prevent cancer.

- For more information, see http://cancergenome.nih.gov/index.asp
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*.
- (E/I) (**NCI**, NHGRI)

Patient Navigation Research Program (PNRP): PNRP is an intervention that addresses barriers to quality standard care by providing individualized assistance to cancer patients and survivors and their families. The program's aim is to decrease the time between a cancer-related abnormal finding, definitive diagnosis, and delivery of quality standard cancer care. PNRP will focus on the four cancers with the greatest disparity in screening and follow-up care: breast, cervical, prostate, and colorectal cancers. Nine PNRPs reach African Americans, American Indians, Asians, Hispanics/Latinos, and rural underserved populations.

- For more information, see http://crchd.cancer.gov/pnp/pnrp-index.html
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCI)

Advances in Oral Cancer Detection: The first product of a current NIH-funded research project to integrate new technologies into a reliable clinical protocol to improve oral cancer detection and survival has reached the market. Researchers report success using a customized optical device that allows dentists to visualize in a completely new way whether a patient might have a developing oral cancer. The simple, handheld device emits a cone of light into the mouth that excites molecules within our cells, causing them to absorb the light energy and re-emit it as visible fluorescence. When the light is removed, the fluorescence disappears. Changes in the natural fluorescence of healthy tissue can indicate light-scattering changes caused by developing tumor cells. Health care providers shine a light onto a suspicious sore in the mouth, look through an attached eyepiece, and check for changes in color. Normal oral tissue emits a pale green fluorescence, whereas early tumor cells appear dark green to black. The instrument is an effective screening adjunct and is useful for helping surgeons determine how far to extend the surgical borders when removing tissue for biopsies.

- For more information, see http://clincancerres.aacrjournals.org/cgi/content/full/12/22/6716
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*.
- (E) (NIDCR)

Promoting Early Detection of Oral Cancer in African American Men: NIH is developing a new series of oral cancer education materials specifically for African American men, who have the highest risk of oral cancer and the lowest 5-year survival rate (only 35.6 percent) of any other population in the United States. This is the first national-level effort of its kind. The first piece in the series, "Are You at Risk for Oral Cancer? What African American Men Need to Know, is now being pre-tested in Washington, DC, Chicago, Los Angeles, and Columbia, South Carolina. The brochure–along with other complimentary education tools, such as fact sheets, posters, and both print and audio public service announcements–will be distributed to African American community groups around the country.

- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E/I) (**NIDCR**, NCI)

Research May Lead to Blood Test to Predict Cancer Treatment Response: In 2007, an estimated 34,000 Americans will be diagnosed with cancer of the oral cavity and pharynx (the middle part of the throat that includes the soft palate, tonsils, and tongue), and 7,550 Americans will die from it. Surgical treatment for these cancers may result in a loss of the ability to speak and swallow. In the largest long-term study of its kind, NIH-supported scientists determined that patients who showed a decline in specific cancer-related proteins after chemotherapy and radiation are more likely to remain in remission. These patients may not need to undergo surgery that may rob them of their speech and swallowing abilities. These findings could help lead to the development of a blood test that enables doctors to detect the recurrence of throat cancer at an early stage. A blood test that enables doctors to closely monitor a patient's rehabilitation while sparing the patient's voice, speech, and swallowing ability is an excellent example of NIH's predictive, preemptive, and personalized approach to medicine.

- Allen C, et al. *Clin Cancer Res* 2007;13:3182-90, PMID: 17545521
- (I) (NIDCD, NCI)

The Dog Genome and Human Cancer: Cancer is the number-one killer of dogs, and studying the major cancers in dogs provides a remarkably valuable approach for developing a better understanding of the development of cancer in humans. The clinical presentation, histology, and biology of many canine cancers very closely parallel those of human malignancies, so comparative studies of canine and human cancer genetics should be of significant clinical benefit to both species. Furthermore, information gained from studying the genetic variant involved in dog size can provide important information for studying cell growth in humans and has the potential to be a useful tool

in cancer research. A 2007 article by NIH's Dr. Elaine Ostrander and colleagues reported a genetic variant that is a major contributor to small size in dogs. In the following month, Dr. Ostrander and colleagues published a study reporting that a mutation in a gene that codes for a muscle protein can increase muscle mass and enhance racing performance in dogs.

- Sutter NB, et al. *Science* 2007;316:112-5, PMID: 17412960
- Mosher DS, et al. *PLoS Genet* 2007;3:e79, PMID: 17530926
- For more information, see http://www.genome.gov/25520294
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (I) (NHGRI)

Salivary Gene Transfer and Therapeutics: Gene transfer may be an ideal strategy to boost salivary production for cancer patients whose salivary glands were damaged during radiation therapy. Although radiation therapy kills cancerous cells, it frequently also destroys the acinar (fluid-producing) salivary gland cells that lie within the salivary gland in grapelike clusters. Patients are unable to produce adequate saliva and suffer a host of long-term problems such as recurrent oral infections and difficulties with swallowing, speech, and taste. Unlike acinar cells, ductal cells in the salivary gland (which can be thought of as the "stems" on the grapes) often survive irradiation. However, they cannot make or secrete saliva. NIH scientists used gene transfer techniques to insert an aquaporin protein gene into the ductal cells; aquaporins are a family of proteins that form pores in cell membranes, through which fluid can pass. Their insertion "plumps up" the stems and allows the flow of fluid into the mouth again. The scientific team has collaboratively and methodically moved this promising idea through the research process, benefiting greatly from the wealth of scientific expertise on the NIH campus. This year, FDA approved the first clinical trial of gene transfer into the salivary glands for cancer patients with dry mouth. Although the outcome of clinical trials is always hard to predict, the preclinical data have been extremely promising.

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (I) (NIDCR)

Cancer.gov in Español: This Spanish-language version of the NCI Web site is designed to reach the Hispanic-Latino population–the fastest growing online audience in the country–to communicate the message that cancer can be prevented and treated and to offer information on all aspects of the disease. The site is specifically tailored for Hispanics and Latinos, and pages are organized around issues of greatest concern. The site will be updated with evidence-based approaches and emerging technologies to ensure that accurate, relevant, and audience-appropriate information is provided. The site demonstrates the commitment to reducing cancer health disparities by making information readily available to underserved populations.

- For more information, see http://www.cancer.gov/espanol
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NCI)

Accomplishments

A Multidisciplinary Approach to Nicotine Addiction: Nicotine addiction is the number-one preventable public health threat and has enormous associated morbidity, mortality, and economic costs. NIH-supported research has generated new knowledge to support the development of more effective prevention messages and treatment approaches. Several notable examples characterize NIH's multidisciplinary approach to targeting the best treatment (or combination of treatments) for nicotine addiction. Genomic studies have recently uncovered a series of genes that are associated with nicotine addiction and that could provide new targets for medication

development and for the optimization of treatment selection. Pharmacologic studies, critical to understanding the basis of nicotine's mode of action, have recently revealed that its addictiveness may hinge upon its ability to slowly shut down or desensitize the brain's response to nicotine. A recent imaging study indicated that a part of the brain called the insula may play an important role in regulating conscious craving. This exciting finding provides a new target for research into the neurobiology of drug craving and for the development of potentially more effective smoking cessation and other addiction treatments. Results of a Phase II clinical trial strongly suggest that a nicotine vaccine, which works by preventing nicotine from reaching the brain, may be a particularly useful tool for cessation programs in the not-too-distant future.

- For more information, see http://www.drugabuse.gov/researchreports/nicotine/nicotine.html
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Clinical and Translational Research*, and Chapter 3: *Genomics*.
- (E) (**NIDA**, NCI) (GPRA Goal)

Developmental Windows of Vulnerability to Environmental Exposures: The Breast Cancer and Environment Research Centers (BCERCs) supported by NIH function as a consortium to study the impact of prenatal to adult environmental exposures that may predispose a woman to breast cancer. The centers bring together basic scientists, epidemiologists, research translational units, and community advocates within and across the centers to investigate mammary gland development in animals and young girls to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. The overall goals of the BCERC are 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. These public health messages will be based on the integration of basic biological, toxicological, and epidemiological data.

- For more information, see http://www.bcerc.org
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (**NIEHS**, NCI) (GPRA Goal)

Clinical Trials Education: The materials in the Clinical Trials Education series represent a collection of over 20 resources developed to increase awareness and participation in cancer prevention and treatment clinical trials. These materials include workbooks, a guide for community outreach, a trainer's guide, online courses for health professionals, DVDs, and slide sets to assist in education programs.

- For more information, see http://www.cancer.gov/clinicaltrials/learning/clinical-trials-education-series
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E/I) (NCI)

Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer Care: NIH supports several research consortia that are designed to enhance understanding of cancer control across the continuum of prevention, screening, and treatment within the context of health care delivery.

- The most comprehensive of these initiatives, the Cancer Research Network (CRN), seeks to improve the effectiveness of preventive, curative, and supportive interventions for major and rare tumors. The CRN consists of the research programs, enrolled populations, and data systems of 13 health maintenance organizations covering care for more than 9 million enrollees, or 3 percent of the U.S. population. This initiative uses a consortium of delivery systems to conduct research on cancer prevention, early detection, treatment, long-term care, and surveillance. Given its large and diverse populations, the CRN is uniquely

positioned to study the quality of cancer care in community-based settings and to explore rare conditions. Seminal research includes CRN research documenting specific gaps in implementing effective tobacco cessation services among clinicians, reasons for late diagnosis of breast and cervical cancers, more rapid uptake in the use of aromatase inhibitors in comparison with tamoxifen in treatment for breast cancer, and examination of the role of a number of common drugs and cancer outcomes using its large and automated pharmaceutical databases.

- In the area of the evaluation of cancer screening in clinical care, the Breast Cancer Surveillance Consortium (BCSC) is a collaborative network of mammography registries linked to tumor and/or pathology registries. The network is designed to assess the delivery and quality of breast cancer screening and related patient outcomes in the United States. Because of the vast size and continually updated clinical information in this research initiative, the BCSC is responsible for research that, for the first time, documented the falling incidence of hormone replacement therapy among screened women; quantified the extent of difference in the association of breast density with breast cancer risk among pre- and postmenopausal women; and determined that, although biopsy rates are twice as high in the United States than in the United Kingdom, cancer detection rates are very similar in the two countries.
- The Cancer Care and Outcomes Research Surveillance Consortium (CanCORS) was established to identify how characteristics of patients, providers, and care delivery systems affect the cancer management and treatment services that patients receive, as well as the relationship between cancer-related clinical practices and outcomes, including patient-centered outcomes such as symptom control and quality of life. CanCORS supports prospective cohort studies on 10,000 patients with newly diagnosed lung or colorectal cancers across geographically diverse populations and health care systems and examines issues related to health outcomes, costs, and patient-centered issues such as symptom control and quality of life.

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

Childhood Cancer Survivors Study (CCSS): Although survival rates from childhood cancers are encouraging, researchers have found that these young survivors may particularly suffer from late effects of treatment. In 2006, CCSS researchers documented serious long-term health issues in adults after radiation for childhood cancers. These findings will change treatment regimen guidelines for current childhood cancers and have implications for individuals from the study who are now adults. The Children's Oncology Group (COG) has prepared a resource for physicians, Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

- For more information, see http://www.cancer.gov/cancertopics/coping/childhood-cancer-survivor-study
- For more information, see http://www.survivorshipguidelines.org
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NCI)

The Centers for Transdisciplinary Research on Energetics and Cancer (TREC): These Centers foster collaboration among transdisciplinary teams of scientists to accelerate progress toward reducing cancer incidence, morbidity, and mortality associated with obesity, low physical activity, and poor diet. The biology and genetics of the many factors that influence diet, physical activity, and obesity across the stages of life are applied to behavioral, sociocultural, and environmental factors, and transdisciplinary training opportunities are provided for scientists. The TREC initiative is interfacing with a number of established NCI initiatives in the area of diet, physical activity,

and weight and is integrated with the NIH Obesity Research Task Force Strategic Plan.

- For more information, see http://cancercontrol.cancer.gov/trec
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NCI)

Transdisciplinary Tobacco Use Research Centers: 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.

- 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) (**NCI**, NIAAA, NIDA)

Reports of the Clinical Trials Working Group (CTWG) and the Translational Research Working Group (TRWG): Recognizing the importance of translational and clinical research, two recently released, major reports of comprehensive evaluations will lead to more rapid progress in translating important research findings into new, effective interventions. The CTWG and TRWG were constituted as broad and inclusive panels (memberships comprise experts from academia, the pharmaceutical industry, advocacy groups, NIH, and other governmental agencies) to review and evaluate the current portfolio of research in this area and to identify ways to synergize, integrate, and coordinate efforts.

- For more information, see http://www.cancer.gov/trwg
- For more information, see http://integratedtrials.nci.nih.gov.
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E/I) (NCI)

Patient and Health Professional Education and Outreach: NIH 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 utilize NIH print and Web-based materials to support their educational programs. 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 (click on "NCI Publications")
- For more information, see http://www.cancer.gov/cancertopics
- For more information, see http://www.cancer.gov/aboutnci/epeco
- For more information, see http://cis.nci.nih.gov
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E/I) (NCI)

Surveillance, Epidemiology, and End Results (SEER) Program and Software Analysis Tools: SEER is an authoritative source of information on cancer incidence and survival in the United States. Publications such as the Annual Report to the Nation on the Status of Cancer, as well as interpretation of recent trends in cancer, inform the public,

researchers, Federal and private agencies, and Congress on national cancer rates and trends. SEER is the only comprehensive source of U.S. population-based information that includes stage of cancer at the time of diagnosis, patient survival, and treatment. Linkage with Medicare and other Federal databases yields information sources that are used routinely to answer major questions on quality, cost, and variability of cancer care, as well as differences by racial and ethnic populations. SEER currently collects and publishes data from approximately 26 percent of the U.S. population. The team is developing computer applications to unify cancer registration systems, analyze and disseminate data, and provide limited access to the public file. SEER is considered the standard for quality among cancer registries around the world.

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

Cancer Control P.L.A.N.E.T.: The Cancer Control P.L.A.N.E.T. (Plan, Link, Act, Network with Evidence-Based Tools) Web portal is a collaboration aimed at providing access to data and resources that can help cancer control planners, health educators, program staff, and researchers design, implement, and evaluate evidence-based cancer control programs. It assists local programs with resources that help them determine cancer risk and cancer burden within their State. It also helps States identify potential partners and provides 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)

The Minority Institution/Cancer Center Partnership (MI/CCP): The MI/CCP provides support for Minority-Serving Institutions (MSI) to partner with Cancer Centers. MI/CCP goals include: (1) increasing the participation of MSIs in the Nation's cancer research and training enterprise, (2) enhancing the number of competitive grant funding from minority investigators, (3) augmenting the research capacity at MSIs, (4) increasing the involvement and effectiveness of the Cancer Centers in research and training relating to ethnic minorities, and (5) developing more effective research, outreach, and education programs that will have an impact on ethnic minority and underserved populations.

- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCI)

Transdisciplinary Tobacco Use Research Centers: 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.

- 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) (**NCI**, NIAAA, NIDA)

Databases for Cervical Cancer Research: NIH has developed data analysis and image recognition tools for studying biomedical images of HPV infection and cervical neoplasia. Image data include 100,000 cervicographs (high-definition cervical photographs), Pap test, and histology images. Tools allow the exploration of visual aspects of HPV and cervical cancer for research, training, and teaching.

- Castle PE, et al. *Cancer Res* 2006;66:1218-24, PMID: 16424061
- Jeronimo J, et al. J *Low Genit Tract Dis* 2006;10:39-44, PMID: 16378030
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (I) (**NLM**, NCI)

Understanding the Interface Between Aging and Cancer: Through a collaborative effort between NIA and NCI, eight NCI-designated Cancer Centers are developing studies on the biology of aging and cancer; patterns of care, treatment efficacy, and tolerance; the effects of comorbidity, prevention, and screening in older persons; and symptom management and palliative care in older patients. This research will help gain insights into why cancer occurs more frequently in older people, whether cancer behaves differently in older adults than in younger people, and how we need to adapt prevention and screening services to reach a greater number of older people as well as to aid in the development of predictive models for tolerance to therapy.

- For more information, see http://www.nci.nih.gov/newscenter/pressreleases/AgingGrants
- (E) (**NCI**, NIA)

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 2007*
- *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2008*

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* (Draft)

Office of AIDS Research (OAR)

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

Other Trans-NIH Plans

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

Summary of Research Activities by Disease Categories

Neuroscience and Disorders of the Nervous System

In 1953, when 27-year-old Henry M. (H.M.) turned to brain surgery to end his struggles with intractable epilepsy, he unwittingly ushered in a new era in research and understanding of memory and the brain. After determining the origin of H.M.'s seizures, neurosurgeon William Scoville removed portions of his brain containing and surrounding a structure called the hippocampus. The operation successfully quieted H.M.'s seizures but left him with profound amnesia–an unintended consequence that fascinates neuroscientists to this day. H.M. retained his former intelligence, his perceptual and motor abilities, and, most notably, his memory of early life events. Yet his recall of new events since the time of the surgery is only fleeting: he still believes he is about 30 years old and, even after many introductions, greets people in his life as though they have never met. Over the last 50 years, some 100 investigators have examined H.M.'s case. Their observations, as well as studies of patients with damage in similar brain regions, including those with Alzheimer's disease, have revolutionized understanding of how memories are formed and where in the brain they are stored. Today, these insights both guide and are extended by human brain imaging studies during learning and memory tasks and by investigations in animals at the level of single neurons and even molecules, leading to the development of drugs to treat memory deficits in people.

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 science, 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. NIH established the Blueprint for Neuroscience Research[11] to reinforce such collaboration and to accelerate neuroscience research through training initiatives and the development of shared tools and resources.

[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.

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, 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 (see the section "Cancer"); 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 (see the section "Life Stages, Human Development, and Rehabilitation").

Brain disorders affecting cognitive, emotional, and behavioral function include schizophrenia and psychoses; autism and other developmental disorders; mood and anxiety disorders; and addiction to nicotine, alcohol, and other substances; as well as posttraumatic 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, and the National Institute of Mental Health (NIMH), 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. The National Eye Institute (NEI) and the National Institute on Deafness and Other Communication Disorders (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, speech and language, taste and smell, and somatosensory function, including the senses of temperature and touch. Although vital to survival, the sensation of pain is also symptomatic of many diseases with origins in and outside the nervous system, from migraine and other headaches to chronic pain in cancer. NIH pain research is led by NIDCR and the NIH Pain Consortium, which coordinates research across NIH on pain and its treatment (see the section "Chronic Diseases and Organ Systems"). 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's syndrome, autism, 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 by 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, neuroscience-related research is supported by NIH in unique populations and environments and on factors contributing to disparities in disease vulnerability and treatment quality and access around the world, such as socioeconomic conditions and infectious disease.

The Burden of Nervous System Disorders

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 over $60 billion[13]. Another 1.4 million Americans sustain a traumatic brain injury each year; it is the leading cause of death and long-term disability in young adults[14]. Traumatic brain injury accounted for an estimated $60 billion in direct medical costs and indirect costs in 2000[15].

Although less often cited as direct causes of mortality, mental disorders result in more disability for U.S. adults than any other class of medical illness[16], and mental illnesses other than drug abuse and addiction account for more than $150 billion in costs annually[17]. In a given year, approximately 12.5 million American adults (or 1 in

---

[12] World Health Organization. Neurological Disorders: Public Health Challenges. Geneva: WHO Press, 2006.

[13] Rosamond W, et al. *Circulation* 2007;115:e69-171, PMID: 17194875

[14] Langlois JA, Rutland-Brown W, Thomas KE. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2006.

[15] Finkelstein E, Corso P, Miller T, et al. *The Incidence and Economic Burden of Injuries in the United States.* New York: Oxford University Press, 2006.

[16] World Health Organization, 2006.

[17] For more information, see http://www.mentalhealthcommission.gov/reports/FinalReport/toc.html

every 17) suffer mental illness symptoms so severe as to cause significant disability[18],[19]. In 2005, 23.2 million Americans needed treatment for an alcohol or illicit drug use problem, and costs related to illicit drug use alone totaled about $180 billion[20]. Nervous system disorders also severely affect the lives of children; an estimated 17 percent of U.S. children have a developmental or behavioral disorder such as autism, intellectual disability, or attention deficit hyperactivity disorder[21].

Demographic trends project an increasing burden from nervous system disorders. In particular, the prevalence of age-related diseases of the nervous system is expected to increase in aging populations benefiting from increased longevity. Current estimates of the number of U.S. adults with Alzheimer's disease range from 2.4 million to 4.5 million, and unless effective interventions are developed, this number is expected to rise almost threefold by 2050[22],[23].

NIH Funding for Neuroscience and Disorders of the Nervous System

In FYs 2006 and 2007, NIH funding for research in neuroscience and disorders of the nervous system was $4.830 billion and $4.809 billion respectively. The table at the end of this chapter indicates some of the research areas involved in this investment (see "Estimates of Funding for Various Diseases, Conditions, and Research Areas").

Summary of NIH Activities

Many common themes reflect shared biological processes found in many aspects of nervous system function and disease. Three such themes–neurodevelopment, neuroplasticity, and neurodegeneration–provide a useful perspective on the broad, multidisciplinary field of neuroscience research and illustrate the dynamic nature of the nervous system across the lifespan. 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, may be found in the bulleted list at the end of this chapter.

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 connections, or

---

[18] Kessler RC, et al. *Arch Gen Psychiatry* 2005;62:617-27, PMID: 15939839

[19] For more information, see http://www.census.gov/popest/national/asrh

[20] Substance Abuse and Mental Health Services Administration. Results from the 2005 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-30, HHS Publication No. SMA 06-4194). Rockville, MD; 2006; For more information, see http://oas.samhsa.gov/NSDUH/2k5NSDUH/2k5results.htm

[21] U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau. The National Survey of Children with Special Health Care Needs Chartbook 2001. Rockville, MD: U.S. Department of Health and Human Services, 2004; For more information, see http://www.cdc.gov/ncbddd/child/improve.htm

[22] Plassman BL, et al. *Neuroepidemiology* 2007;29:125-32, PMID: 17975326

[23] Hebert LE, et al. *Arch Neurol* 2003;60:1119-22, PMID: 12925369

synapses, between neurons, each step in nervous system development is vulnerable to disruption by disease, injury, or environmental exposures. Each also has implications for normal neurological, mental, and behavioral function and for health and disease risk across the lifespan.

Human brain development continues into early adulthood and proceeds at different rates in different brain areas and pathways. Understanding normal nervous system development is essential to identifying when, where, and how developmental processes can go wrong. To this end, NIH-supported investigators are applying advanced brain imaging technologies to large-scale studies of human brain development in healthy children and adolescents. For example, in the NIH Magnetic Resonance Imaging (MRI) Study of Normal Brain Development, extramural researchers at seven collaborating institutions are collecting brain scans and clinical and behavioral data from more than 500 infants, children, and adolescents over the course of 7 years. Data gathered and analytical tools developed for this longitudinal study will be available to the broader research community in a Web-based, searchable database.

As another example, in the largest longitudinal pediatric neuroimaging study to date (829 MRI scans from 387 subjects, ages 3 to 27 years), intramural NIH scientists have reported different trajectories of brain development in males and females, finding that brain volume peaks earlier in girls than in boys. Such studies of normal brain development and maturation are providing scientists with important baseline data that will help them identify signs of atypical development as well as factors that may be associated with disease risk later in life. Moreover, understanding the developmental course of different brain areas can help to explain behavioral and cognitive development and its consequences for mental health and disease risk. For instance, previous brain imaging studies have suggested that brain pathways that are important for decision-making and impulse control are among the last to fully mature. This aspect of brain development may contribute to impulsive behavior in teenagers and help explain their increased susceptibility to drug abuse and addiction.

In a remarkable feat of nervous system development, the estimated 100 billion neurons in the human brain are wired together into networks that underlie brain functions, from sensory perception, to learning and memory, to motor control. Insight into the wiring diagrams of these networks and the developmental processes that lead to their establishment promises to unlock some of the most fundamental questions in neuroscience research. Indeed, certain brain diseases, including schizophrenia and autism, are hypothesized to involve aberrant development of brain connectivity. Research in this area benefits from new technologies for manipulating and visualizing neurons in experimental animal models, in which neuronal connections are established and organized according to rules similar to those found in the human nervous system. In one recent example, NIH-supported scientists developed a technique that can label thousands of direct synaptic connections received by individual neurons in the rat brain. By enabling neuroscientists to map neuronal networks, such experimental techniques will help show how changes in brain function and behavior can result from changes in these networks, whether they occur during normal development and learning or as a consequence of injury or disease.

One salient feature of the developing nervous system is its heightened sensitivity to external influences. Although crucial for shaping the proper development of many brain pathways and their corresponding sensory, motor, cognitive, and emotional functions, this heightened sensitivity also makes the developing nervous system especially vulnerable to potentially damaging environmental factors. These factors include exposures to toxins, viral infections, nutritional deficits, traumatic events, and social experiences throughout life. For instance, prenatal exposure to alcohol can lead to fetal alcohol syndrome (FAS), a devastating developmental disorder characterized by lifelong nervous system impairments that may include intellectual and learning disabilities, and behavioral and social deficits. NIH supports a broad research portfolio on FAS and its diagnosis, treatment, and prevention. A growing area of neuroscience research focuses on how genetic and environmental factors interact in nervous system development, function, and disease. The interplay between external influences and genetic predispositions

appears likely to contribute to a range of disorders, such as depression and other mood and anxiety disorders, addiction, multiple sclerosis, Parkinson's disease, and autism. As one example of research in this area, NIH supports several efforts to understand how autism spectrum disorders may arise from the combined effects of genetic vulnerabilities and exposure to harmful environmental agents during key periods of development. Ongoing projects co-funded by NIH and the Environmental Protection Agency (EPA) are looking for biomarkers of these disorders and for differences in immune system function that may increase susceptibility to potential environmental triggers.

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 or be affected by changes in the body's internal environment and external conditions and events. This capacity, known as *plasticity*, results in changes in the electrical activity and composition of neuronal networks. Plasticity 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.

Neuroplasticity enables beneficial adaptations, including acquiring new knowledge, improving performance on practiced tasks, and adjusting behavior based on positive or rewarding consequences. A recent NIH-funded study demonstrated how such adaptive plasticity might be exploited for therapeutic intervention. In this study, using real-time brain imaging, patients with chronic pain learned 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. Unfortunately, plasticity can also be maladaptive. Accumulating evidence from NIH-supported research indicates that the same brain mechanisms that mediate reward-related learning are involved in the development of addiction and compulsive overeating. Continued research into how plasticity contributes to addiction and other mental disorders may lead to intervention strategies that reverse or prevent these mechanisms.

Neuroplasticity also plays a role in many aspects of epilepsy, a class of disorders characterized by abnormal bursts of electrical activity (seizures) in networks of neurons that can lead to odd sensations, emotions, behaviors, convulsions, muscle spasms, and loss of consciousness. Basic neuroscience studies on the plasticity of synaptic connections and brain circuits are showing how epileptic activity emerges and how seizures themselves can in turn cause plasticity in affected circuits, often increasing the probability of seizure recurrence. In addition to these basic science studies, NIH supports translational research and clinical trials of potential anticonvulsant therapies, including extensive efforts through the NIH Anticonvulsant Screening Program, a drug discovery program that conducts state-of-the-art evaluations to determine both potential efficacy and toxicity of preclinical candidate compounds in validated epilepsy model systems. NIH also works with the epilepsy community to develop and pursue benchmarks for research to prevent and treat epilepsy and co-occurring disorders.

Harnessing the capacity of the nervous system to adapt by activating its intrinsic mechanisms for repair and plasticity offers great hope for restoring function in the injured or diseased brain and spinal cord. For example, after spinal cord injury, neurons near the site of damage sprout new nerve fibers. Although this sprouting is limited in the absence of intervention, an understanding of the mechanisms that guide and restrict such spinal plasticity may allow neuroscientists to design strategies that integrate the new nerve fibers into spinal circuitry, replacing damaged connections and promoting functional recovery. In addition, NIH has long supported a program to develop neural prostheses, devices that restore functions that have been lost due to injury or disease, as in deafness or paralysis from spinal cord injury. The success of neural prostheses depends not only on their ability to bypass or replace injured components of the nervous system, but also on their integration into remaining functional circuits, which relies on plasticity mechanisms.

Stem cells are another promising source of plasticity and repair in the nervous system, and although many challenges and questions remain in this young area of research, basic and translational neuroscience studies are making progress in advancing stem cell-based therapies toward the clinic. During early embryonic development, stem cells have the potential to become any cell type in the body; as development proceeds, the range of potential fates narrows, depending on the tissue generating the cells. Beyond early development, stem cell production and neurogenesis–the generation of new neurons–occurs only in restricted regions of the brain. One active area of basic neuroscience research examines the role of neural stem cells in normal function and the brain's response to injury and disease, and the potential for treatments that tap into this intrinsic renewal mechanism. Other stem cell research in neuroscience focuses on the development of therapies in animal models that transplant stem cells into the damaged or diseased nervous system. Transplanted cells may be embryonic stem cells or other non-neuronal stem cells, they may be engineered to become certain desired cell types, or they may be designed to express specific genes that could act to promote recovery or repair or restore genetic deficits. As part of the Quantum Grants Program designed to make profound advances in health care, NIH has recently funded research to engineer implants from neural and vascular stem cells and innovative biomaterials to provide a source of cells for tissue repair in an animal model of stroke.

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. Although recent and ongoing research continues to yield exciting insights into the biological and environmental causes of neurodegenerative disorders, much remains unexplained, and while some interventions alleviate disease symptoms, none currently exists that can halt progressive degeneration.

Aging is the most consistent risk factor for developing a neurodegenerative disorder, and many of the 50 million adults in the United States who are older than age 60 are at substantial risk for cognitive impairment and emotional disorders from many causes as they age. The trans-NIH Healthy Brain Project focuses on demographic, social, and biologic determinants of cognitive and emotional health in aging adults. The risk for degenerative disorders affecting sensory systems also increases with age, leading to hearing and visual impairments. Building on a previous demonstration that antioxidant supplements could slow age-related macular degeneration (AMD), the leading cause of blindness in the elderly, a large-scale NIH study is assessing the benefits of other supplements and dietary changes on AMD and cataracts.

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, and scientists now believe that damage to the brain begins well before symptoms appear. Basic science studies have identified genetic factors and protein abnormalities that contribute to neuronal dysfunction and death in Alzheimer's disease. NIH also funds 29 Alzheimer's Disease Centers, which carry out clinical studies and other research on Alzheimer's and related degenerative diseases (see Chapter 4). 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, which involves nearly 70 sites in the United States and Canada. Ongoing trials include the Docosahexaenoic Acid trial, which is examining whether treatment with DHA, an omega-3 fatty acid, will slow decline in patients with Alzheimer's disease. Observational studies have shown a reduced risk of Alzheimer's disease associated with DHA consumption, and animal studies have shown that DHA reduces brain levels of beta-amyloid, oxidative damage associated with beta-amyloid, and neurotoxicity. Recent research has also shown that an extract from the leaf of the *Ginkgo biloba* tree reduces neuronal pathology and symptoms in an animal model of the disease, and NIH is supporting the largest clinical trial to date to test the

effectiveness of *Ginkgo biloba* in preventing dementia in humans. Additional research supported through the Alzheimer's Disease Neuroimaging Initiative aims to identify biomarkers and develop imaging technologies to aid early diagnosis, which may enable more targeted and timely interventions.

Neurodegenerative disorders are often associated with degeneration in specific populations of neurons or regions of the nervous system. For example, Parkinson's disease results in the loss of a class of dopamine-producing neurons in the substantia nigra, a part of the brain important for motor control. NIH-funded scientists recently described a mechanism in substantia nigra neurons that contributes to their selective vulnerability and that, like the disease itself, becomes more prevalent with age. Manipulations to "rejuvenate" the neurons by blocking this mechanism promoted their survival, suggesting a new potential target for drug development. NIH also supports 14 Morris K. Udall Centers for Excellence in Parkinson's Disease Research and engages with the Parkinson's disease research community to identify and pursue research opportunities.

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 (see Chapter 4), as well as other efforts to translate basic science findings to the clinic. 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. NIH-supported scientists recently reported the first genetic risk factors for multiple sclerosis to be identified in more than 20 years (see also the section "Autoimmune Diseases" in this chapter). These studies benefited from new technologies in genetic research that allow simultaneous analysis of many thousands of genetic variations, or polymorphisms, across the entire genome. Such genome-wide studies are giving scientists unprecedented insight into disorders that result from the combined effects of many genetic variations and their interactions with environmental influences.

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. Today's fast global communication and the power and storage capacity of modern computer systems are enabling collaborative research on increasingly large scales. A major priority of the NIH Blueprint for Neuroscience Research is to facilitate research by funding the creation of shared resources and tools for scientists. Examples include a publicly available atlas of gene expression in the mouse brain and spinal cord across the lifespan, a clearinghouse for informatics tools and resources for brain imaging applications, and an effort to develop common measures of neurological and behavioral function for use in clinical trials and epidemiological and longitudinal studies. NIH also supports several data registries, databases, and tissue consortia for neurological diseases and mental disorders that offer shared access to genetic and clinical data and biological samples. Genome-wide and other genetic studies using such materials are identifying genes that contribute to bipolar disorder, that influence the effectiveness of antidepressant therapies, and that predispose individuals to drug abuse and addiction (see also the section "Genomics" in Chapter 3).

Collaborative approaches are also transforming clinical and translational research in neuroscience, which build on advances and knowledge gained through basic science studies to develop treatments and interventions for disease in people. NIH supports seven centers as part of the Specialized Program of Translational Research in Acute Stroke, a national network of research centers established to develop acute stroke therapies from preclinical research through early-phase clinical trials. These centers also work to improve prehospital stroke care, participate in community education, and develop telemedicine to expand rapid access to acute stroke care. NIH also supports the Silvio O. Conte Centers for the Neuroscience of Mental Disorders, which integrate and translate basic and

clinical neuroscience research on severe mental illnesses, such as schizophrenia and mood disorders. As another example, the Spinal Muscular Atrophy (SMA) Project is a new translational approach to preclinical drug development, motivated by the recent discovery of the gene defect that causes this degenerative disease that affects motor neurons of the spinal cord. With expertise from NIH as well as FDA, academia, and industry, the SMA Project has created a multisite enterprise for accelerated drug development.

Scientific research is an increasingly global endeavor, and because brain disorders are the leading contributors to disability in almost all parts of the world, global capacity for neuroscience research is essential. Through a program entitled Brain Disorders in the Developing World, NIH supports innovative, collaborative programs to build sustainable neuroscience research capacity in low- and middle-income nations. Projects focus on some of the unique challenges facing neuroscience research in the developing world and on topics that are relevant worldwide, including the neurological consequences of infectious diseases and nutritional deficits. For example, one study suggests that a form of the APOE4 gene, which is associated with an increased risk for developing Alzheimer's disease, may have a protective effect early in life against the negative consequences of malnutrition. This finding may help elucidate mechanisms to protect the brain and body during times of nutritional deficit.

Looking to the Future

NIH-supported neuroscience research is steadfastly advancing its mission to reduce the burden of nervous system disorders. New technologies that allow neuroscientists to observe and manipulate neuronal networks could provide insights into how neural activity leads to complex brain functions. Continued innovation in neuroimaging techniques may identify disease risk or presence early, enabling more rapid diagnosis and intervention. With knowledge gained through large-scale genetic and epidemiological studies, clinicians of the future may personalize preventive and therapeutic strategies according to the genetic profile and lifestyle of individual patients. Future medications for treating nervous system disorders may reach specific brain targets with ease, and advances in neuroprostheses may more successfully restore motor, sensory, and cognitive function after disease or injury. These are just a few of the possibilities to come as NIH-supported neuroscience research continues to build on past progress and identify and pursue new opportunities. A glimpse into the future might reveal the ability to replenish damaged nerve cells, reprogram neuronal connections that support addiction, and stop degenerative processes that rob millions of their thoughts and memories.

Notable Examples of NIH Activity

Key for Bulleted Items:

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported through a congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = Concerns progress tracked under the **G**overnment **P**erformance and **R**esults **A**ct

Neurodevelopment: Periods of Growth, Maturation, and Vulnerability

Research on Environment and Autism: NIH has several innovative research studies aimed at understanding how autism and autism-spectrum disorders may arise from a combination of genetic vulnerability and exposure to harmful environmental agents during key periods of early development. The NIEHS/EPA Children's Center for

Environmental Health at the University of California, Davis supports a highly integrated research program spanning human-to-animal cellular models to explore the interplay of immune, genetic, and environmental factors in autism susceptibility. In 2001, this center launched the first and most comprehensive large-scale epidemiological investigation of environmental exposures and susceptibility factors for autism, the Childhood Autism Risk from Genes and Environment (CHARGE) study. Scientists are exploring how persistent organic pollutants such as polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) may contribute to neurological development disorders such as autism by interacting with cellular epigenetic mechanisms that control timing and patterns of gene expression. NIH also supports an exploratory study at Johns Hopkins University to develop new methods to measure individual differences in the immunotoxicity of mercury.

- For more information, see http://www.vetmed.ucdavis.edu/cceh
- (E/COE) (NIEHS)

Autism Centers of Excellence (ACE): In 2007 and 2008, NIH created the unified ACE program in order to maximize coordination and cohesion of NIH-sponsored autism research efforts. The ACE programs will focus on a broad range of autism-related research, including but not limited to neuroimaging, biomarkers and susceptibility genes, pharmacotherapy, early intervention, and risk and protective factors.

- For more information, see Chapter 4: *NIH Centers of Excellence*.
- (E) (**NIMH**, NICHD, NIDCD, NIEHS, NINDS)
- (COE)

National Database for Autism Research (NDAR): NDAR is a collaborative biomedical informatics system being created by NIH to provide a national resource to support and accelerate research in autism.

- 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)

Genomic Studies of Autism: NIH has supported a number of studies that are pointing to potential genetic causes of autism.

- For more information, see http://www.nimh.nih.gov/press/gene-mutations-autism.cfm
- For more information, see http://www.nimh.nih.gov/press/largest-ever-search-for-autism-genes-reveals-new-clues.cfm
- For more information, see http://www.nimh.nih.gov/press/autismmetgene.cfm
- For more information, see http://www.nimh.nih.gov/press/moy-crawley-autism.cfm
- This example also appears in Chapter 3: *Genomics.*
- (E) (**NIMH**, NCRR, NICHD, NINDS)

New Genetics Tools Shed Light on Addiction: NIH-supported research is taking full advantage of the massive databases and rapid technologies now available to study how genetic variations influence disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms and genetic predispositions underlying diseases like addiction. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases by using custom screening tools known as “gene chips” (e.g., the *neurexin* gene has been found to play a role in drug addiction). A next-generation “neurochip” is being developed with 24,000 gene variants related to substance use and other psychiatric disorders. Applying this tool to addiction

and other brain disorders will advance 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 (i.e., a "pharmacogenetic" approach). To complement these efforts, NIH is investing heavily in the emerging 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. A focus on gene-by-environment interactions has recently been expanded to incorporate developmental processes, which are now known to also affect the outcome of these interactions. The resulting Genes, Environment, and Development Initiative (GEDI) seeks to investigate how interactions among these factors contribute to the etiology of substance abuse and related phenotypes in humans.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/rfa-da-07-012.html
- For more information, see http://nihroadmap.nih.gov/roadmap15update.asp
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development.*
- (E/I) (**NIDA**, NCI, NIAAA, NIMH)
- (GPRA Goal)

Underage Drinking Research Initiative: In 2004, NIH launched the 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 development. Activities and accomplishments in 2007 include:

- Provided the scientific foundation for *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking* (released March 6, 2007) and for the ongoing work of the Interagency Coordinating Committee on Preventing Underage Drinking
- Convened scientific meetings of experts, including the Underage Steering Committee that met four times over a 2-year period, a Meeting on Diagnosis of Alcohol Use Disorders Among Youth (April 2006), and a Meeting on Screening for Child and Adolescent Drinking and AUDs Among Youth (June 2007)
- Issued three Requests for Applications (RFAs), including "Underage Drinking: Building Health Care System Responses" (four projects awarded in FY 2006), "Impact of Adolescent Drinking on the Developing Brain" (five projects awarded in FY 2007), and "Alcohol, Puberty, and Adolescent Brain Development" (three projects awarded in FY 2007).
- Published Alcohol Research & Health, Vol. 28, Number 3: *Alcohol and Development in Youth: A Multidisciplinary Overview*
- Published a supplement of seven developmentally focused papers covering a broad range of underage drinking topics (accepted for the journal Pediatrics).

- 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*, Chapter 2: *Life Stages, Human Development, and Rehabilitation,* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (NIAAA)

Prenatal Alcohol, Sudden Infant Death Syndrome, and Stillbirth (PASS) Research Network: Following a 3-year feasibility study, the NIH established this 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 will

prospectively 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) (**NICHD**, NIAAA)

The Role of Development in Drug Abuse Vulnerability: NIH supports a number of longitudinal studies at various stages of development, following cohorts over extended timeframes. Information is gathered on children's cognitive and emotional development, as well as their vulnerability to addiction later in life. These studies have been critical to estimate, for example, the contribution of in utero drug exposure to emotional and cognitive development, vulnerability to substance abuse, and other mental disorders. This knowledge, together with animal studies that provide complementary and validating information while minimizing the confounding factors that are likely to play a role in prenatal effects of drug exposure in humans, will help us to mitigate the deleterious impact of substance abuse on the developing fetus. With regard to later developmental stages, the application of modern brain imaging technologies has generated unprecedented structural and functional views of the dynamic changes occurring in the developing brain (from childhood to early adulthood). The discovery of these changes has been critical to understanding the role of brain development in decision-making processes and responses to stimuli, including early exposure to drugs. Such studies have suggested, for example, that an unbalanced communication between volitional control and emotional circuits may explain some of the impulsive reactions typical of adolescents, who tend to engage in risky behaviors and are at heightened risk for developing addictions. Collectively, these longitudinal studies, using new imaging and genetics tools, promise a greatly enhanced ability to interpret the effects of myriad environmental variables (e.g., quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics) on brain development and behavior.

- For more information, see http://www.drugabuse.gov/NIDA_notes/NNvol19N3/Conference.html
- For more information, see http://www.nida.nih.gov/NIDA_notes/NNvol19N3/DirRepVol19N3.html
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (**NIDA**, NICHD) (GPRA Goal)

MRI 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, as well as clinical and behavioral data to understand normal brain development in approximately 500 children across the Nation. This large-scale, longitudinal study uses several state-of-the-art brain-imaging technologies. The data will be disseminated as a Web-based, user-friendly resource to the scientific community.

- Evans AC, et al. *Neuroimage.* 2006;30:184-202, PMID: 16376577
- 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* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E/I) (**NICHD**, NIDA, NIMH, NINDS)

Studies of Normal Brain Development: The NIH Intramural Research Program is conducting studies to explore

brain development in healthy children and adolescents with MRI. Recent studies have addressed brain structure differences related to risk for Alzheimer's disease and sex differences in brain development trajectories.

- Shaw P, et al. *Lancet Neurol* 2007;6:494-500, PMID: 17509484
- Lenroot RK, et al. *Neuroimage* 2007;36:1065-73, PMID: 17513132
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (NIMH) (GPRA Goal)

Powerful New Technique Reveals How Brain Cells Wire Together: In order to understand how the brain processes visual information and performs other tasks, researchers have wanted to construct a "wiring diagram" of the billions of neurons connected in precise, identifiable circuits. A breakthrough technology has helped clear this major hurdle by revealing all the connections made by a single nerve cell. The new tool uses a modified rabies virus, which can spread indefinitely through the nervous system by jumping between communicating nerve cells. However, scientists modified the virus so that it jumps once and then leaves a fluorescent tag in the neurons connected to a single cell. This permits visualization of functional processing circuits in living brains. It can also be used in transgenic mice to deactivate targeted classes of neurons expressing specific genes, revealing changes in brain function, including behavior.

- Wickersham IR, et al. *Neuron* 2007;53:639-47, PMID: 17329205
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*
- (E) (NEI)

Neuroplasticity: Substrates for Change and Repair

Promising Approaches to Treating Chronic Pain: Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can produce drug dependence. Thus, an area of enormous need is the development of potent non-opioid analgesics. In recognition of this, NIH has implemented an aggressive and multidisciplinary research program. Many of these initiatives are yielding tangible results that stand to revolutionize the field of pain management. At the molecular level, cannabinoid (CB) research has shown that it is possible to selectively activate the CB system to provide analgesia with minimal or no psychotropic side effects or abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different receptors, the targeting of which could provide a vastly expanded range of pharmacotherapeutic effects. 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 a non-neuronal brain cell type, glia, has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their pro-inflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of 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.

- For more information, see: http://www.nida.nih.gov/whatsnew/meetings/default.html
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (**NIDA**, NINDS)

Tools to Reveal the Mechanisms Governing Behavior: Newly acquired but rapidly evolving tools and techniques that monitor or probe discrete brain systems have allowed NIH-supported researchers to begin filling in the information gap between molecular or cellular events and behavioral outcomes. A notable preclinical example of

this trend is the development of a genetically engineered method to turn the electrical impulses of brain cells on and off with pulses of light–in sync with the split-second pace of real-time neuronal activity. The novel technique borrows genes from light-responsive algae and bacteria to unravel the intricate workings of brain circuits with extreme precision. This powerful new tool could be used to assess the role of neuronal activity in regulating normal behavior and disease processes. On the clinical side, an array of brain imaging devices has produced much information on how neural circuits develop and process information under normal conditions and how they become impaired by a disease like addiction. These advances have led to the fertile concept that the transition from abuse to addiction is not a switch but a gradual degradation of the ability of different circuits to "talk" to each other as they attempt to compensate for their deficiencies. Interestingly, these studies are also showing significant overlap in the circuits involved in drug abuse and the circuits underlying compulsive overeating and obesity. Moreover, in preclinical studies, compounds that interfere with food consumption in animal models of compulsive eating also interfere with drug administration.

- For more information, see http://www.nimh.nih.gov/press/lightsswitchneurons.cfm
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development.*
- (E) (**NIDA**, NIMH)

The Scientific Basis of Acupuncture: Ongoing research on acupuncture includes a substantial portfolio of basic and translational studies employing state-of-the-art neuroimaging technology. This work is beginning to provide powerful scientific insight into the potential neurobiological mechanisms of action by which acupuncture might work. Clinical trials of acupuncture for a number of medical conditions are also under way, including studies examining (1) the potential role of traditional acupuncture as an additive/alternative treatment for the prevention of acute cardiac events in patients with coronary artery disease, (2) whether manual or electro-acupuncture contributes to neurological recovery after spinal cord injury, and (3) the efficacy of acupuncture in relieving post-thoracotomy pain syndrome (severe and persistent aching or burning pain along surgical scars in the chest).

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (NCCAM)

Cochlear Implants: One of the more groundbreaking biomedical achievements in the last 30 years has been the cochlear implant, an electronic device that provides a sense of sound to individuals who are profoundly deaf or severely hard-of-hearing. Cochlear implants process sounds from the environment and directly stimulate the auditory nerve, bypassing damaged portions of the inner ear. Nearly 100,000 individuals worldwide have been fitted with cochlear implants. In the United States, approximately 22,000 adults and nearly 15,000 children have received them. Derived in part from NIH-funded research that dates back to the early 1970s and continues today, this remarkable technology has enabled deaf and severely hard-of-hearing individuals to enjoy an enhanced quality of life. NIH-supported scientists showed that profoundly deaf children who receive cochlear implants at an early age develop language skills at a rate comparable to that of children with normal hearing. They also found that the benefits of the cochlear implant in children far outweigh its costs. Scientists can now study the large groups of children who were identified early for hearing loss and use this knowledge to document how treatments such as cochlear implants can lead to improved speech and language acquisition, academic performance, and economic outcomes for these children.

- Nicholas JG, Geers AE. *Ear Hear* 2006;27:286-98, PMID: 16672797
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development.*

- (E) (NIDCD)

Neurobiology of Appetite Control: NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. Examples include research on how serotonin reduces appetite; the actions of the protein mTOR in sensing nutrients in the body so as to modulate food intake; and a strategy to block ghrelin, a stomach-secreted hormone that signals the brain to increase food intake. This research has implications for new therapies for obesity.

- Cota D, et al. *Science* 2006;312:927-30. PMID: 16690869
- Heisler LK, et al. *Neuron* 2006;51:239-49, PMID: 16846858
- Zorrilla EP, et al. *Proc Natl Acad Sci U S A* 2006;103:13226-31, PMID: 16891413
- For more information, see http://tinyurl.com/22o9mv ("Obesity" chapter)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*
- (E) (NIDDK)

A Multidisciplinary Approach to Nicotine Addiction: Nicotine addiction is the number-one preventable public health threat and has enormous associated morbidity, mortality, and economic costs. NIH-supported research has generated new knowledge to support the development of more effective prevention messages and treatment approaches. Several notable examples characterize NIH's multidisciplinary approach to targeting the best treatment (or combination of treatments) for nicotine addiction. Genomic studies have recently uncovered a series of genes that are associated with nicotine addiction and that could provide new targets for medications development and for the optimization of treatment selection. Pharmacologic studies, so critical to understanding the basis of nicotine's mode of action, have recently revealed that its addictiveness may hinge upon its ability to slowly shut down or desensitize the brain's response to nicotine. A recent imaging study indicated that a part of the brain called the insula may play an important role in regulating conscious craving. This exciting finding provides a new target for research into the neurobiology of drug craving and for the development of potentially more effective smoking cessation and other addiction treatments. Results of a Phase II clinical trial strongly suggest that a nicotine vaccine, which works by preventing nicotine from reaching the brain, may be a particularly useful tool for cessation programs in the not-too-distant future.

- For more information, see http://www.drugabuse.gov/researchreports/nicotine/nicotine.html
- This example also appears in Chapter 2: *Cancer,* Chapter 3: *Genomics,* and Chapter 3: *Clinical and Translational Research.*
- (E) (**NIDA**, NCI) (GPRA Goal)

Treatments to Fight Methamphetamine Addiction: The abuse of methamphetamine–a potent and highly addictive psychostimulant–is a serious problem in the United States. Methamphetamine abuse can have devastating medical, psychological, and social consequences. Adverse health effects include memory loss, aggression, psychotic behavior, heart damage, and abnormal brain function. Methamphetamine abuse also contributes to increased transmission of hepatitis and HIV/AIDS and can spawn increased crime, unemployment, and other social ills. The good news is that methamphetamine abuse and addiction are treatable, and people do recover. As methamphetamine abuse has increased, so has NIH's support of research to combat it, including research on genetics, brain development, and translation of findings. This research has led to the development of two effective behavioral therapies for methamphetamine addiction: (1) the Matrix Model, consisting of a 16-week program that includes group and individual therapy and addresses relapse prevention, behavioral changes, establishment of new drug-free environments, and other areas, and (2) Motivational Incentives for Enhanced Drug Abuse Recovery, a cost-effective incentive method for cocaine and methamphetamine addiction that has been shown to sustain abstinence in twice the number of participants engaged in treatment as usual. Increasingly,

community treatment providers nationwide are implementing motivational incentives as part of drug addiction treatment.

- For more information, see http://www.drugabuse.gov/ResearchReports/Methamph/Methamph.html
- For more information, see http://www.drugabuse.gov/Testimony/6-28-06Testimony.html
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIDA)

Quantum Program: The NIH Quantum Grants Program has been developed to make a profound (quantum-level) advance in health care by funding research, over two phases, on targeted projects that will develop new technologies for the diagnosis, treatment, or prevention of a major disease or national public health problem. The first of the Quantum Grants was to engineer stem cell-based neurovascular regenerative units in a laboratory environment, which can then be implanted into the damaged cortex of stroke patients to provide a source of neural and vascular cells that will continue to develop and differentiate. This approach may lead to the first true treatment for stroke, which is one of the most common causes of disability and severely affects the quality of life of patients throughout the world. Another Phase I Quantum competition was completed in September 2007, with four additional grants awarded. The Phase II Quantum competition will begin in FY 2009.

- For more information, see http://www.nibib.nih.gov/Research/QuantumGrants
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NIBIB)

Prevention of Trauma-Related Mental Disorders in High-Risk Occupations: NIH is supporting a research initiative to develop and test preemptive interventions to prevent trauma-related disorders, such as posttraumatic stress disorder, among occupational groups at high risk for trauma exposure, such as the military, firefighters, police, and rescue workers.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-010.html
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIMH)

Traumatic Brain Injury Program: Traumatic brain injury (TBI) presents enormous challenges to neuroscience because of the numbers of people affected and the range of problems TBI can cause. The consequences of TBI may be subtle or severe, immediate or delayed, perhaps even predisposing to problems many years later in life. TBI can compromise virtually any human ability, depending on which parts of the brain are damaged. NIH supports a broad program of research, from studies of how TBI causes immediate and delayed damage to brain cells, to development of measurable diagnostic markers of damage, through large clinical trials to test interventions. NIH clinical studies are developing both emergency interventions to minimize damage and rehabilitation strategies to compensate for damage or encourage the brain to adapt. The high rate of TBI among military personnel in Afghanistan and Iraq presents a special concern. NIH intramural scientists are working with the Departments of Defense and Veterans Affairs to study the psychobiological consequences of TBI among military personnel, and NIH is working with all relevant Federal agencies to coordinate research activities on high-priority issues, including a 2006 interagency conference on TBI and follow-up meetings in 2007 and 2008 focusing on issues such as injury classification and potential combination therapies.

- (E/I) (NINDS, NICHD)

Epilepsy Research Benchmarks: In March 2000, NINDS convened a broad group of scientists, clinicians, people impacted by epilepsy, and public policymakers for a White House-initiated conference on the disorder. After this conference, NINDS developed a series of epilepsy research goals in three major topic areas: (1) interrupting and monitoring the development of epilepsy, (2) preventing epilepsy, and (3) developing more effective therapies. The Institute worked with the epilepsy research and patient communities to develop a series of benchmarks for tracking progress toward these goals. Researchers have made substantial progress since this meeting, and science has also evolved over this time. As a result, NINDS organized a session at the most recent Curing Epilepsy 2007 conference for the participants to discuss revisions to the first set of benchmarks. NINDS is currently collecting public feedback on these revised goals and will work with a group of representatives from the scientific community to refine the benchmarks for release at the 2007 American Epilepsy Society meeting.

- For more information, see http://www.ninds.nih.gov/funding/research/epilepsyweb/index.htm
- (E) (NINDS)

Neural Prosthesis Program: 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. The NINDS Neural Prosthesis program pioneered the development of this technology beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants for the hearing impaired, 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 standing and voluntary bowel and bladder control after spinal cord injury, to allow paralyzed persons to control devices directly from their brains, and to control seizures. Ongoing research also seeks to improve cochlear implants and to advance 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 that now includes private-sector companies and represents a cooperative effort among several NIH Institutes, which coordinate their efforts with programs now under way in the Department of Veterans Affairs and the Department of Defense.

- For more information, see http://www.ninds.nih.gov/funding/research/npp/index.htm
- 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**, NCRR, NEI, NIBIB, NICHD, NIDCD)

Link Between Eye Movement and Reward: Dopamine is vital to motor behaviors, but neurons that release dopamine carry signals related to rewards, not body movements. As a solution to this puzzle, recent theories propose that the reward-related dopamine signals are used for learning of motor behaviors. However, it is unknown how dopamine neurons acquire the reward-related signals. NIH scientists have shown that a small brain area called the lateral habenula controls dopamine neurons by inhibiting them and thereby suppressing less rewarding eye movements. This discovery opens up new research connecting emotion and motivation to motor behaviors.

- Matsumoto M, Hikosaka O. *Nature* 2007;447:1111-5, PMID: 17522629
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (I) (NEI)

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. Recent animal studies have identified several genes that alter sensitivity to alcohol and may provide targets for medications development.

- Researchers have discovered a genetic mutation that disrupts the function of the fruit fly gene RhoCAP18B, causing the flies to be much more resistant to alcohol sedation. Other variants of the same gene, each of which has a distinctly different effect on the response to alcohol, were subsequently identified.

    - Rothenfluh A, et al. *Cell* 2006;127:199-211, PMID: 17018286
    - Another fruit fly gene, homer, has been shown to be required for normal sensitivity and tolerance to alcohol. This study shows that ethanol sensitivity and tolerance co-map to the same population of neurons, suggesting that the neuronal circuits controlling these two behaviors, known to contribute to alcohol dependence, are shared.

        - Urizar NL, et al. J *Neuroscience* 2007;27:4541-51, PMID: 17460067
        - This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
        - (E) (NIAAA)

Increased Endocannabinoid Signaling Increases Ethanol Consumption and Decreases Acute Ethanol Intoxication: Endocannabinoids, the naturally occurring substances in the brain that act on the same receptors as the active ingredients of marijuana, have been discovered to play a role in regulating appetite for alcohol. NIH-supported scientists discovered that mice lacking expression of fatty acid amidohydrolase (FAAH), the main endocannabinoid-degrading enzyme, showed an increased appetite for ethanol, decreased sensitivity to ethanol-induced sedation, and faster recovery from ethanol-induced motor incoordination. These results show that impaired FAAH function leads to increased voluntary alcohol intake and point to FAAH both as a potential susceptibility factor and a therapeutic target for excessive alcohol consumption.

- Hansson AC, et al. *Neuropsychopharmacol* 2007;32:117-26, PMID: 16482090
- Blednov YA, et al. *Neuropsychopharmacol* 2007;32:1570-82, PMID: 17164820
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E/I) (NIAAA)

Re-innervation of Regenerated Hair Cells: Hair cells detect sound and are named for the hairlike projection from their top surface. Researchers hope one day to regenerate hair cells in the inner ears of people who have experienced damage due to noise, drugs, or disease. However, the ability to regrow hair cells will not restore hearing or balance without properly reconnected nerve endings. NIH-supported scientists used drugs to destroy hair cells and corresponding nerve endings in adult pigeons. (Unlike mammals, birds and other vertebrates are able to regenerate hair cells naturally.) Using a high-powered microscope, the scientists examined tissue sections and determined that the re-innervation process was similar to the pattern observed during normal nerve cell development. Although the regenerated nerve endings were less complex than those generated in normal development, many balance-related behaviors nevertheless fully recovered. This finding suggests that scientists may need only to regenerate simple nerve endings to restore the sense of balance. Further clarification of the mechanisms involved in nerve cell regeneration is essential for the potential recovery of balance and hearing in people with inner-ear damage.

- Zakir M, Dickman JD. *J Neurosci* 2006;26:2881-93, PMID: 16540565

- (E) (NIDCD)

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

Alzheimer's Disease Neuroimaging Initiative (ADNI): ADNI is an innovative public-private partnership for examining the potential for serial MRI, positron emission tomography (PET), or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease. Early results suggest that researchers may be able to reduce the costs associated with clinical trials by improving imaging and biomarker analysis. One ADNI study found that a standard model can be used to monitor the performance of MRI scanners at multiple clinical sites, ensuring the accuracy of the MRI images. In another study, investigators compared changes over time in PET scans of brain glucose metabolism in people with normal cognition, mild cognitive impairment, and Alzheimer's disease and found that scans correlated with symptoms of each condition and that images were consistent across sites. This finding suggests that PET scans may be a valid method for monitoring the effectiveness of therapies in future clinical trials. More than 200 researchers have already accessed a public database containing thousands of brain images and related clinical data obtained through blood and cerebrospinal fluid analyses.

- For more information, see http://www.loni.ucla.edu/ADNI
- For more information, see http://www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials/ADNI.htm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (**NIA**, NIBIB)

Genome-Wide Genotyping in Parkinson's Disease: NIH researchers recently conducted genome-wide genotyping of publicly available samples from a cohort of 267 patients with Parkinson's disease and 270 neurologically normal control subjects to identify any common genetic variability with significant effect on the risk for Parkinson's disease. The project has produced approximately 220 million data points in the 537 subjects, the largest collection of publicly available genotypes in a case-control cohort. The release of these data facilitates research on Parkinson's disease and other neurodegenerative disorders, and the genotypes from neurologically normal control subjects can be used as a comparison cohort for other studies, dramatically reducing the cost of future research.

- Fung HC, et al. *Lancet Neurol* 2006;5:911-6, PMID: 17052657
- For more information, see http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20060927parkinsons.htm
- This example also appears in Chapter 3: *Genomics.*
- (E/I) (**NIA**, NINDS)

Ongoing Research on Complementary and Alternative Medical Approaches for Patients with Alzheimer's Disease or Dementia and Their Caregivers:

- A study in an animal model of Alzheimer's disease, evaluating whether fish oil, a safe and relatively inexpensive dietary supplement source of omega-3 fatty acids, shows similar or better effects than docosahexaenoic acid (DHA) in slowing the progression of changes associated with cognitive and functional decline in humans with Alzheimer's disease
- A feasibility study of polarity therapy as an intervention for family caregivers of people with dementia who experience high levels of stress and are at risk for physical and mental health illness
- Preclinical investigations of the potential activity and mechanisms of effect of (1) D-pinitol, a natural compound found in high concentrations in pine tree components and in smaller but significant concentrations in soy, and (2) substances derived from heat-processed ginseng and other related natural products.

- (E) (NCCAM)

Alzheimer's Disease Cooperative Study (ADCS): Much of the NIH-supported clinical research on Alzheimer's disease takes place through the ADCS. The study involves a consortium of centers in the United States and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of Alzheimer's disease or predict the disease's development in vulnerable people. To date, approximately 4,600 people have participated in the trials. In FY 2007, new studies included a trial to demonstrate whether intravenous immunoglobulin is clinically useful for treating Alzheimer's disease and a trial to examine whether treatment with docosahexaenoic acid, an omega-3 fatty acid, will slow cognitive decline in patients with Alzheimer's disease.

- For more information, see http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20061017ADCS.htm
- For more information, see http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/NeuroscienceOfAging/ProgramInitiatives/ADCS.htm.
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NIA)

Parkinson's Disease Registry: NIEHS has begun to address the need for more precise data on the incidence and prevalence of Parkinson's disease through support of a Parkinson's disease registry in the State of California, where the large and diverse population, coupled with the wide range of exposures that exist through agriculture and other activities, provides a unique opportunity to investigate disease-environment links. The United States does not have a national health registry to supply data on Parkinson's disease, so estimates are based on sampling by individual studies in specific locales. The Parkinson's registry in California will allow us to base national estimates on a registry drawing upon a cross-section of the population in our most populous state.

- For more information, see http://www.thepi.org/site/parkinson/section.php?id=101
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems.*
- (E) (NIEHS)

Multiple Sclerosis: Although the exact cause of multiple sclerosis is unknown, research suggests a strong genetic component. NIH funds a number of studies to determine the underlying genetic causes of multiple sclerosis, including a project to identify regions of the genome containing multiple sclerosis susceptibility genes using a large familial dataset and genomic analysis tools. NIH also funds clinical trials to test therapies for multiple sclerosis, including the CombiRx trial, a randomized, controlled clinical trial comparing the efficacy of treatment combining beta-interferon and glatiramer acetate versus treatment with a single agent for relapsing forms of MS. A study conducted in conjunction with CombiRx by NIH intramural researchers (BioMS) is assessing multiple sclerosis biomarkers by using genomic and proteomic technology and relating the information obtained back to clinical and MRI data generated by the CombiRx clinical trial.

- Gregory SG, et al. *Nat Genet* 2007;39:1083-91, PMID: 17660817
- International Multiple Sclerosis Genetics Consortium, et al. *N Engl J Med* 2007;357:851-62, PMID: 17660530
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research.*
- (E/I) (NINDS)

Age-Related Eye Disease Study, Part 2 (AREDS2): Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly in the United States and will be an increasing burden in future years, based on demographics. The original AREDS, which was completed in 2005, demonstrated that antioxidant vitamin and mineral supplements reduced the progression to advanced AMD by 25 percent. Building on these landmark findings, AREDS Part 2 (AREDS2) is assessing additional supplements (lutein, zeaxanthin, and long-chain omega-3

fatty acids) as a treatment for AMD and cataracts. AREDS2 is also evaluating effects of eliminating beta-carotene and/or reducing zinc in the original AREDS formulation on AMD progression. AREDS2 investigators will also explore gene-environment interactions in the development of these conditions, cognitive function, and cardiovascular health.

- For more information, see http://www.areds2.org
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (**NEI**, NIA)

Retinal Neurodegeneration Program: The Retinal Neurodegeneration Program is a new multidisciplinary intramural research program that combines basic, preclinical, and translational research to develop and test therapeutic interventions in several retinal degenerative diseases. These interventions include gene therapy, small molecules, neurotrophic factors, and cell-based systems, in combination with a variety of treatment delivery technologies.

- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (I) (NEI)

Alzheimer's Disease Genetics Initiative and Data Storage: Only one of the four validated Alzheimer's disease genes, *APOE*, has been definitively linked with the more common late-onset form of the disease. A fifth gene, *SORL1*, has recently been linked with late-onset Alzheimer's disease in some studies. The goal of the Alzheimer's Disease Genetics Initiative is to develop the resources necessary for identifying the late-onset Alzheimer's disease risk factor genes and the interactions of genes with the environment. In FY 2006, NIH achieved its goal to recruit 1,000 families with two or more siblings living with Alzheimer's disease through an unprecedented alliance of Alzheimer's disease centers, researchers, and outreach with the Alzheimer's Association. To facilitate access by qualified investigators, all genetic data derived from NIH-funded studies on late-onset Alzheimer's disease genetics are deposited at a central data storage site at Washington University in St. Louis, another NIH-approved site, or both. Discovery of risk factor genes will help illuminate the underlying disease processes of Alzheimer's disease, open up novel areas of research, and identify new targets for drug therapy.

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

Understanding the Mechanisms of Alcohol-Induced Tissue Injury: Heavy alcohol use has an impact on nearly every organ system of the body (the most vulnerable being the brain and liver), and the resulting pathological conditions contribute to increased mortality and morbidity among all age and racial/ethnic groups and both sexes. NIH is especially interested in elucidating mechanisms of injury common to multiple body and organ systems. A number of Program Announcements and RFAs have been issued to support research to increase our understanding of the underlying cellular and molecular mechanisms of tissue injury caused by alcohol consumption, including alcohol's genetic, epigenetic, and metabolic effects. The long-term goals of these initiatives are to identify biomarkers for alcohol exposure and for the early detection of alcohol-induced tissue injury, as well as to develop new therapeutics that control or modify outcomes of chronic alcohol use.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-065.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-360.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-361.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-004.html

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-005.html
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems,* Chapter 2: *Life Stages, Human Development, and Rehabilitation,* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E/I) (NIAAA)

Cognitive and Emotional Health Project: The Healthy Brain: The purpose of this initiative is to assess the state of longitudinal and epidemiological research on determinants of cognitive and emotional health in aging adults. The project has completed a comprehensive review of measures that have been (or could be) used in epidemiological research. To help NIH learn what epidemiological data exist on the cognitive and emotional health of adults in the United States, the project polled investigators who are conducting these types of studies and created an online database. In addition, a Critical Evaluation Study Committee conducted an analysis and published a summary of the existing scientific literature pertaining to factors involved in the maintenance of cognitive and emotional health in adults. NIH is discussing new initiatives to expand this project, including promoting the use of existing datasets and developing ancillary studies to examine how cognitive and emotional health influence each other.

- For more information, see http://www.alzheimersanddementia.com/article/S1552-5260(05)00503-0/abstract?articleId
- For more information, see http://trans.nih.gov/cehp
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (**NINDS**, NIA, NIMH)

Progress in Parkinson's Disease Research: For the past 7 years, NIH has been actively 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. NIH has also 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.

- 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
- (E) (NINDS)

Toward Better Treatment for Muscular Dystrophy: Activities funded by NIH are pursuing multiple pathways to therapeutic development for the muscular dystrophies. NIH funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, designed to accelerate the translation of fundamental scientific advances to the clinic (see Chapter 4). NIH also recently funded two large-scale translational research projects in muscular dystrophy: one to develop small-molecule drugs for Duchenne and potentially other forms of muscular dystrophy and another to develop the optimal vector for vascular delivery of genes. A new NIH Government Performance and Results Act (GPRA) goal aims to advance two emerging strategies for treating muscular dystrophy to clinical trial readiness by 2013. The Muscular Dystrophy Coordinating Committee's *Action Plan for the Muscular Dystrophies* also identified therapy development goals to be pursued by NIH and the committee's partner agencies and organizations. A recent workshop convened by NIH reviewed the status of different therapeutic approaches for muscular dystrophy and discussed ways to move this research forward.

- For more information, see http://www.ninds.nih.gov/find_people/groups/mdcc/MDCC_Action_Plan.pdf
- For more information, see www.wellstonemdcenters.nih.gov
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (COE) (**NINDS**, NIAMS, NICHD) (GPRA Goal)

Translational Research on Alzheimer's Disease: To move basic research on Alzheimer's disease 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. To closely monitor the progress of the translational projects, provide guidance, and foster interactions among investigators involved in translational research funded by these programs, NIH staff will hold the First Annual Investigators Meeting for Translational Research in September 2007.

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

Preclinical Efficacy of Ginkgo biloba in Alzheimer's Disease: NIH-supported investigators recently published results showing that Ginkgo biloba, studied in an animal model of Alzheimer's disease, reduces both the formation of the specific brain abnormalities seen in humans and the resulting paralysis seen in the animals. These experiments lend additional support to the hypothesis that Ginkgo biloba may be useful in slowing the progression of Alzheimer's disease. That hypothesis is being tested in the largest clinical trial to date of Ginkgo biloba for the prevention of dementia, supported by NIH.

- Wu Y, et al. *J Neurosci* 2006;26:13102-13, PMID: 17167099
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NCCAM)

Inflammatory Factor Mediates Nerve Degeneration in Glaucoma Model: In glaucoma, elevated eye pressure plays a role in damaging fibers in the optic nerve, which relays visual signals to the brain. However, the link between pressure and nerve damage is not well understood. Recent research in mice suggests a critical role for the protein tumor necrosis factor-alpha (TNF-a) in developing glaucoma. A molecular target in the glaucoma disease pathway opens up doors for drug therapy.

- Nakazawa T, et al. *J Neurosci* 2006;26:12633-41
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NEI)

Gene Expression Changes in Facioscapulohumeral Muscular Dystrophy: Results from a genome-wide scan of skeletal muscle biopsies suggest a link between eye blood vessel defects and muscle defects that characterize facioscapulohumeral muscular dystrophy. Patient participants were recruited from the National Registry for Myotonic Dystrophy and patients with facioscapulohumeral muscular dystrophy and their family members.

- Osborne RJ, et al. *Neurology* 2007; 68:569-77. PMID: 17151338
- For more information, see http://www.niams.nih.gov/Funding/Funded_Research/registries.asp#dystrophy
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Genomics.*
- (E) (**NIAMS**, NCRR, NINDS)

Hereditary Hearing Loss: NIH recognizes that one of the most rapidly developing areas of research is functional genomics, which involves determining the identity, structure, and function of genes. Hereditary or genetic causes account for approximately 50-60 percent of the severe to profound cases of childhood hearing loss. NIH-supported scientists are working to understand the normal function of these genes and how they are altered in individuals with hereditary hearing loss. At present, more than 70 genes causing nonsyndromic hereditary hearing impairment have been mapped to intervals on particular chromosomes; many of these efforts were the result of collaborations involving NIH-supported scientists. In collaborative efforts with scientists in Colombia, India, Indonesia, Israel, Lebanon, Mexico, Newfoundland, Pakistan, Tunisia, Puerto Rico, and the United States, NIH is accelerating this gene discovery effort. These research investments to understand the genetic basis of communication disorders will help scientists develop diagnostic tests and better treatments for the millions of Americans with hereditary hearing impairment.

- Morton CC, Nance WE. *N Engl J Med* 2006;354:2151-64, PMID: 16707752
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E/I) (NIDCD)

Advancing Neuroscience Research Through Collaboration

The NIH Blueprint for Neuroscience Research: The NIH Blueprint is a collaborative framework that brings 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 2006, the Blueprint launched initiatives to develop new neuroimaging technologies, a clearinghouse to distribute and improve existing neuroimaging software, core resource centers, a neurological and behavioral assessment tool, and new genetically modified mouse models. The Blueprint also supported training programs in neuroimaging, computational neuroscience, and translational research. In FY 2007, the Blueprint released funding announcements to identify biomarkers for neurodegeneration, develop new ways to deliver therapeutics to the nervous system, and provide interdisciplinary training in neurodegeneration research.

- For more information, see http://www.neurosciencebluprint.nih.gov
- This example also appears in Chapter 3: *Research Training and Career Development.*
- (E) (**NINDS**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, OBSSR)

A Clearinghouse for Neuroimaging Informatics Tools and Resources: NIH understands that researchers seeking neuroimaging analysis software tools need a convenient way to find and compare useful software. Indeed, the best or most suitable neuroimaging analysis technologies for research may be hidden in someone's laboratory or some obscure corner of cyberspace. NIH is creating a Neuroimaging Informatics Tools and Resources Clearinghouse. The 14 NIH ICs that participate in the Neuroscience Blueprint have supported the development of sophisticated, high-quality neuroimaging informatics tools and resources. The clearinghouse is intended to facilitate the dissemination of those tools and resources and promote their adoption within the extended neuroimaging community. A contract has been awarded to create the clearinghouse infrastructure. The infrastructure will include a Web site that will not only provide access to tools and resources but will also provide ongoing opportunities for public comment to guide future development and enhancement of the tools. In addition to the contract award, grant awards are being made to individual extramural scientists to enable them to render their tools more suitable for this initiative. The awards will fund the enhancement of tools to make them easier to use, more broadly applicable, or more compatible with other existing tools. The clearinghouse was released to the public in October 2007.

- For more information, see http://www.nitrc.org

- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems.*
- (E) (**NIBIB**, NCCAM, NCRR, NEI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

NIMH Genetics Repository: Over the last 9 years, NIMH has built the infrastructure for large-scale genetics studies through the NIMH Human Genetics Initiative. Through this Initiative, NIMH established a repository of DNA, cell cultures, and clinical data that serve as a national resource for researchers studying the genetics of complex mental disorders.

- For more information, see http://nimhgenetics.org.
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems.*
- (E) (NIMH)

Practical Clinical Trials: NIH has completed primary and secondary phases of several practical clinical trials that have examined treatment effectiveness for mental disorders such as schizophrenia, bipolar disorder, and depression. The infrastructure developed for each of these large multisite trials–involving more than 10,000 participants at over 200 sites–has forged efficient, effective, and collaborative relationships between scientists and clinicians throughout the country. To capitalize on the national networks established for the trials, NIH will fund infrastructure-only support for the platform of clinical sites and an administrative core. It is anticipated that the platform will serve as a critical foundation for supporting participant enrollment, facilitating communication among trial sites, maintaining up-to-date training in diagnosis and treatment, and providing needed administrative organization.

- For more information, see http://www.nimh.nih.gov/healthinformation/catie.cfm
- For more information, see http://www.nimh.nih.gov/healthinformation/stard.cfm
- For more information, see http://www.nimh.nih.gov/healthinformation/stepbd.cfm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIMH)

NINDS Human Genetics Repository: In 2003, 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 2007, the repository held material from 16,683 subjects, including those with stroke (4,363), epilepsy (1,065), Parkinson's disease (3,585), and motor neuron diseases such as ALS (2,445), as well as control samples (4,767). The ethnically diverse collection represents populations from the United States and several other countries. Investigators have submitted or published more than 50 scientific articles based on data from this resource, and technological advances allowing "whole genome screening" for disease genes have also 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)

NIH Pain Consortium: The aims of the NIH Pain Consortium are to enhance pain research and promote collaboration among researchers across the many NIH ICs that have programs and activities addressing pain. The consortium held its second annual symposium, "Advances in Pain Research," on May 1, 2007, to feature new and exciting advances in pain research and pain management. Topics included neuropathic pain, visceral pain, inflammatory pain, and treatment-induced pain. Participants included NIH and extramural scientific communities, health care providers, and the public. Consortium ICs also issue an NIH-wide Funding Opportunity Announcement,

"Mechanisms, Models, Measurement, and Management in Pain Research," to encourage pain research and delineate cross-cutting NIH interests in pain.

- For more information, see http://videocast.nih.gov/PastEvents.asp
- For more information, see http://painconsortium.nih.gov/index.html
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*
- (E/I) (**NIDCR**, CC, FIC, NCCAM, NCI, NCRR, NIA, NIAAA, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIGMS, NIMH, NINDS, NINR, OBSSR, OD, ODP/ORD, ORWH, OTT)

Gene Expression Nervous System Atlas (GENSAT): Knowing where and when genes are active is a key to understanding how the nervous system develops, how the normal brain works, and what goes wrong in disease. More than half of all genes are active at some point in the brain, yet only a small fraction of these have been well characterized. To systematically address this issue, NIH initiated the GENSAT project. The project prescreens the activity of many genes at four developmental time points in several parts of the brain and spinal cord and, for genes of high interest, generates strains of mice in which a visible marker is turned on wherever and whenever the gene of interest is active. In addition to the value of the publicly accessible GENSAT database, the mice are useful for research on normal development and function and diseases. For example, researchers used GENSAT mice to discover that one of two previously indistinguishable types of nerve cells is selectively vulnerable in Parkinson's disease. By revealing the molecular mechanism that kills the cells, these experiments also identified a new potential drug target. GENSAT is now a resource within the NIH Neuroscience Blueprint and will expand to include nerve cells in the eye, ear, and pain pathways.

- Day M, et al. *Nat Neurosci* 2006;9:251-9, PMID: 16415865
- For more information, see http://www.gensat.org/index.html
- For more information, see http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=search&db=gensat
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (**NINDS**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, OBSSR)

Programs to Accelerate Medications Development for Alcoholism Treatment: Alcoholism is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ from one drinker to another. 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 their 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 have already produced several targets for human studies that are now under way, such as rimonabant, a cannabinoid CB1 receptor blocker, and antalarmin, a corticotropin-releasing factor receptor blocker.
- 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 human trials network.

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

The Collaborative Study on the Genetics of Alcoholism (COGA): In its 18th 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) who are densely affected by alcoholism. Investigators have identified several genes, including *GABRA2, ADH4, ADH5,* and *CHRM2,* 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.

- For more information, see http://zork.wustl.edu/niaaa
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems,* Chapter 3: *Genomics,* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NIAAA) (GPRA Goal)

Brain Disorders in the Developing World: Research Across the Lifespan: Brain disorders are the leading contributor to years lived with disability in all regions of the world, with the exception of sub-Saharan Africa. This program boosts research in the developing world on childhood disorders such as cerebral palsy and epilepsy, on mental illnesses such as depression and schizophrenia, and on degenerative disorders, such as stroke and Alzheimer's disease. Under this program, U.S. investigators and their foreign collaborators are studying the neurocognitive consequences of HIV/AIDS, the relationship between zinc nutrition and brain development, and the neurological disorders stemming from treatable infectious causes, such as cerebral malaria, cisticercosis, tuberculosis (TB), and bacterial sepsis.

- For more information, see http://www.fic.nih.gov/programs/research_grants/brain_disorder
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (**FIC**, NEI, NIA, NIAAA, NICHD, NIDA, NIEHS, NIMH, NINDS, ODS)

Trans-NIH Chronic Fatigue Syndrome Research: NIH coordinates chronic fatigue syndrome research through a trans-NIH Working Group on Research on Chronic Fatigue. This working group developed an action plan to enhance the status of chronic fatigue syndrome research at the NIH and among the external and intramural scientific communities. The working group held a workshop on grantsmanship in FY 2007 to provide researchers with an overview of funding opportunities, an understanding of the NIH funding process, and an opportunity to meet with program officials. In addition, the Office of Research on Women's Health and a subset of the working group ICs issued an RFA in FY 2006 to explicate how the brain, as the mediator of the various body systems involved, fits into the schema for understanding chronic fatigue syndrome. This RFA solicited proposals from multidisciplinary teams of scientists to develop an interdisciplinary approach to the study of chronic fatigue syndrome in men and women across the lifespan and resulted in seven new research projects on chronic fatigue syndrome.

- For more information, see http://orwh.od.nih.gov/cfs.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-002.html
- For more information, see http://orwh.od.nih.gov/cfs/2006NIHfundedCFSstudies.html
- For more information, see http://orwh.od.nih.gov/cfs/cfsFundingGMWs.html
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*

- (E) (**ORWH**, NIAID, NIAMS, NIAAA, NIA, NICHD, NIDA, NIDDK, NINDS, NCRR, CSR, NIEHS, NIDCR, NINR, NHLBI, NIMH, NCCAM, FIC, ODS, OBSSR)

Mechanisms of HIV Neuropathogenesis: Domestic and Global Issues: Neurological manifestations, including HIV dementia and opportunistic infections and tumors, are among the most threatening complications of HIV infection. Emerging data indicate that the prevalence of HIV-related neurological disease differs across regions of the world, suggesting that different subtypes of HIV may be more or less capable of causing neuropathology, or that genetic variance among people in various regions of the world could affect susceptibility to HIV's neuropathological effects. NIH sponsored a meeting in the spring of 2007 to address these issues, resulting in the release of a funding announcement.

- For more information, see http://synapse.neurology.unc.edu/venice
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-030.html
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense.*
- (E) (**NIMH**, NINDS, OAR)

National NeuroAIDS Tissue Consortium (NNTC): The NNTC is a repository of brain tissue and fluids from highly characterized HIV-positive individuals. Established as a resource for the research community, NNTC includes information from more than 2,000 individuals, including approximately 641 brains, thousands of plasma and cerebrospinal fluid samples, and additional organs and nerves of interest.

- For more information, see http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-08-021.html
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems.*
- (E/I) (**NIMH**, NINDS)

NIH Countermeasures Against Chemical Threats (CounterACT) Research Network: 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, is entering clinical trials in epilepsy patients through the NINDS 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.

- For more information, see http://www.ninds.nih.gov/funding/research/counterterrorism/index.htm
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense.*
- (E) (**NINDS**, NEI, NIAID, NIAMS, NIEHS, NIGMS)

Specialized Program of Translational Research in Acute Stroke (SPOTRIAS): The objective of 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 seven SPOTRIAS sites, which have made substantial progress, including impressive increases in the use of the "clot buster" tPA (tissue plasminogen activator) to treat acute stroke; the establishment of three interlinked repositories for protein and DNA tissue samples, neuroimages, and clinical data; enrollment of more than 640 individuals with acute stroke into treatment protocols; the management of 17 early-phase clinical trials; and the training of 25 research fellows.

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

The SMA Project: A decade ago, spinal muscular atrophy (SMA) was one of hundreds of poorly understood inherited disorders that affect the nervous system, and the outlook for developing treatments was bleak. The discovery of the gene defect that causes SMA dramatically improved prospects, revealing a rational strategy to develop drugs. The SMA Project is a novel approach to preclinical drug development and may serve as a model for other disorders. The project has brought together expertise from industry, academia, the FDA, and NIH to generate a detailed drug development plan. A "virtual pharma organization" develops and applies the resources to carry out the plan through subcontracts to companies that serve the pharmaceutical industry. The project created a new drug through extensive modification of indoprofen, a drug with known activity in experimental settings that was not suitable for clinical application. Through repeated modification and evaluation cycles in laboratory tests, the project produced hundreds of chemical compounds related to indoprofen and has made encouraging progress. In 2007, preclinical studies began to evaluate the two best candidates for clinical readiness. The best of these will likely be ready for early stage clinical testing in 2008 or 2009. In early 2008, the project also began two new drug development projects that could yield additional drug candidates for SMA.

- For more information, see http://www.smaproject.org
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NINDS)

The NIH Toolbox for Assessment of Neurological and Behavioral Function: The NIH Blueprint for Neuroscience Research supports this contract awarded to the Evanston Northwestern Healthcare Research Institute. The project entails the development of a set of standardized neurological and behavioral measures of cognition, emotion, sensation, and motor function. The toolbox will foster uniformity among the basic measures used and allow comparisons or data compilations across multiple studies. This innovative approach to measurement will be responsive to the needs of researchers in a variety of settings and will place particular emphasis on measuring outcomes in clinical trials and functional status in large cohort studies, such as epidemiological and longitudinal studies.

- For more information, see http://grants.nih.gov/grants/guide/notice-files/NOT-AG-06-008.html
- For more information, see http://www.enh.org/aboutus/press/article.aspx?id=4358.
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (**OBSSR**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR)

The NIH Rapid Access to Intervention Development (RAID) Pilot Program: The NIH- RAID Pilot program makes available, on a competitive basis and at no cost to investigators, certain critical resources needed to develop new small-molecule drugs, including not only laboratory services but also expertise in the regulatory process. The program directly addresses roadblocks to moving research findings from bench to bedside. Among the projects approved are drugs for hepatic fibrosis, the blood diseases beta-thalassemia and sickle cell anemia, brain tumors, and the neurological disorders Friedreich's ataxia and Alzheimer's disease. The NIH-RAID Pilot program is part of the NIH Roadmap for Medical Research.

- For more information, see http://nihroadmap.nih.gov/raid/index.aspx
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (Roadmap–all ICs participate)

Gene Influences Antidepressant Response: Whether depressed patients will respond to an antidepressant

depends, in part, on which version of a gene they inherit. In an NIH-supported study, investigators found that having two copies of one version of a gene that codes for a component of the brain's mood-regulating system increased the odds of a favorable response to an antidepressant by up to 18 percent, compared to having two copies of the other, more common version.

- For more information, see http://www.nimh.nih.gov/press/stardgene.cfm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
- (E) (NIMH)

Genetic Roots of Bipolar Disorder Revealed by First Genome-Wide Study of Illness: According to NIH-funded research, the likelihood of developing bipolar disorder depends in part on the combination of small effects of variations in many different genes in the brain, none of which is powerful enough to cause the disease by itself.

- For more information, see http://www.nimh.nih.gov/press/mcmahon-bipolar-genetics.cfm
- This example also appears in Chapter 3: *Genomics.*
- (E) (NIMH)

Other Notable Activities

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

- *Drug Development for Cognitive Impairments in Schizophrenia:* The Treatment Unit for Research on Neurocognition in Schizophrenia program is a network that is testing the safety and efficacy of new therapeutic compounds for treating the cognitive deficits of schizophrenia.

  - (E) (NIMH)

- *Studies of Fragile X Syndrome:* NIH has entered into a public-private partnership to study and test possible medications for treating fragile X syndrome, the most common cause of inherited mental impairment. Fragile X syndrome is caused by a single gene mutation that ultimately results in exaggerated activity of a brain protein called mGluR5. Researchers will study, in animals, the safety of chemical compounds known to block this mGluR5 activity. If this phase goes well, researchers will move forward with clinical studies.

  - (E) (NIMH, NINDS, NICHD)

- *Faster-acting depression treatments:* A recent NIH-funded study found that people with treatment-resistant depression experienced relief in as little as 2 hours after a single intravenous dose of ketamine, a medication usually used in higher doses as an anesthetic. Used in very low doses, ketamine is important for depression research but at higher doses could have side effects that may limit its clinical use. Nevertheless, this research could inform the development of faster and longer acting medications for treating depression.

  - For more information, see http://www.nimh.nih.gov/press/ketamine.cfm
  - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
  - (I) (NIMH)

Clinical Research and Trials in Neurological Disease: NINDS provides extramural funding for more than 1,000 clinical research studies. Nearly 1 million people participate in these projects, and it is essential to assess the return on this investment in improving quality of life. NINDS contracted an independent evaluation of the costs and benefits of its Phase III clinical trials. Investigators found that, although the total cost of clinical trials in the study was $335 million, the cumulative benefits over a 10-year period exceeded $15 billion and added 470,000 healthy years of life to people in the United States. NINDS is extending this evaluation approach by developing a computer model that will estimate the public health impact of any given clinical trial in neurology or neurosurgery. This model will be publicly available for use by researchers and the Institute to facilitate decision-making. NINDS is also assessing ways to further improve its trials. To this end, the Institute has funded a Neurological Emergencies Treatment Trials (NETT) Network to facilitate high-quality clinical trials in acute neurological disorders and accelerate the implementation of new therapies into practice in emergency departments.

- Johnston SC, et al. *Lancet* 2006;367:1319-27, PMID: 16631910
- For more information, see http://www.nett.umich.edu/nett/welcome
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NINDS)

Scientific Basis of the Placebo Effect: The placebo effect can be defined as the measurable, observable, or felt changes that occur during, but are not directly attributable to, a specific health intervention. It is a ubiquitous and frequently powerful phenomenon that operates in all forms of medicine, so good clinical research is designed to account for its effects as well as those of the intervention under study. Because of the power of the placebo effect, it is equally important to understand the mechanisms by which it operates and to explore how its benefits might be maximized to enhance the quality and effectiveness of all forms of health care. An ongoing NIH initiative is examining multiple aspects of the placebo effect through interdisciplinary investigations employing molecular, physiological, biochemical, immunological, genetic, behavioral, and social science approaches. This work is beginning to shed light on many facets of the placebo effect. For example, one recently published study showed that placebo-associated pain relief was correlated with activation of areas of the brain that are associated with pain relief that occurs through both innate mechanisms and with use of opioid narcotics. Other ongoing studies are examining the role and importance of the placebo effect in the relationship between patient and health care provider.

- Zubieta JK, et al. *J Neurosci* 2005;25:7754-62, PMID: 16120776
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (NCCAM)

Reducing Disparities in Stroke: NIH is actively 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 the prevalence of risk factors for stroke and on stroke incidence and mortality. To date, researchers have recruited approximately 27,000 of a projected 30,000 individuals (about 50 percent African American and 50 percent White) and have already published a number of important findings on their baseline data. NIH has also established an acute stroke research and care center at the Washington Hospital Center, 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 the use of tissue plasminogen activator among minorities. The program directly addresses GPRA Goal SRO-8.9.2: “By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities.”

- For more information, see http://www.regardsstudy.org/index.htm
- This example also appears in Chapter 2: *Minority Health and Health isparities.*
- (E/I) (NINDS)

Blending Initiative: Bench to Bedside to Community: Efforts to systematically move science-based interventions and practices into community settings are exemplified in the testing of drug abuse treatment approaches in the community settings where they will be used by drug treatment professionals who are trained to implement them. This work is occurring through the National Drug Abuse Treatment Clinical Trials Network at NIH, which involves practitioners from community treatment programs in formulating research protocols and provides real-world feedback on their success and feasibility. The adoption of the addiction medication buprenorphine by a growing number of community treatment programs that treat patients with opioid addiction is an example of real culture change issuing from NIH clinical research. A similar approach is under way to enhance treatment for drug-addicted individuals involved with the criminal justice system through research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) initiative. CJ-DATS seeks to achieve better integration of drug abuse treatment for criminal offenders with other public health and public safety forums and is a collaborative effort by NIH and multiple Federal agencies and health and social service professionals. These initiatives are helping to change the culture of how drug abuse treatment is delivered in this country.

- For more information, see http://www.drugabuse.gov/CTN
- For more information, see http://www.cjdats.org
- For more information, see http://www.drugabuse.gov/Blending
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems,* Chapter 3: *Clinical and Translational Research,* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (NIDA) (GPRA Goal)

Hearing Aids and Directional Microphones: Approximately 32.5 million American adults report some degree of hearing loss, according to data from the National Center for Health Statistics 2003 National Health Interview Survey. Although almost 95 percent of Americans with hearing loss could have their hearing treated with hearing aids, only about 20 percent of Americans with hearing loss have hearing aids, and many who wear them are dissatisfied with them. Hearing in noisy environments is a major unsolved problem faced by hearing aid users, and of all available technologies, directional microphones currently show the most promise for addressing this problem. NIH-supported scientists have been studying the tiny fly *Ormia ochracea*, which has such sensitive directional hearing that it has inspired ideas for a new generation of hearing aids. The fly's ear structure, which permits ultrasensitive time coding and localization of sound, provides a model for scientists and engineers in developing new miniature directional microphones for hearing aids that can focus sound amplification on speech. To improve hearing aid technology so that users can better understand speech in a noisy background, NIH-supported scientists successfully completed a prototype of a low-power, highly directional microphone small enough to fit into a hearing aid. The use of improved directional microphones in hearing aids will improve the quality of life for individuals with hearing loss who depend on hearing aids to understand spoken language.

- Miles RN, Hoy RR. *Audiol Neurootol* 2006;11:86-94, PMID: 16439831
- This example also appears in Chapter 3: *Technology Development.*
- (E) (NIDCD) (GPRA Goal)

Visual Processing in Neuroscience Blueprint: Much of the cerebral cortex of the brain is devoted to processing the images that flood our eyes. The visual cortex also connects with many regions of the brain that govern memory, language, movement, and a myriad of other cognitive abilities. NIH's visual processing research portfolio prioritizes understanding of how the brain processes visual information, how brain activity results in visual perception, and how the visual system interacts with other cognitive systems.

- For more information, see http://www.neuroscienceblueprint.nih.gov
- For more information, see www.nei.nih.gov/funding/app.asp
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NEI)

Centers on Suicide Prevention: In response to the 2002 Institute of Medicine Report "Reducing Suicide: A National Imperative," NIH issued an RFA and funded three centers focused on suicide intervention and prevention. Now in their third year of support, the centers have conducted pilot intervention studies with patients suffering from mental and substance use disorders.

- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (**NIMH**, NIAAA, NIDA)

Understanding How Prefrontal Cortex Affects Cognitive Function: In FY 2008, NIH will support an RFA to stimulate research on how a brain region called the prefrontal cortex interacts with other parts of the brain to give rise to sophisticated behavior and cognitive function. Abnormal functioning of the prefrontal cortex is associated with mental disorders such as schizophrenia and depression.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-110.html
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NIMH)

Brain Tumor: The NIH Brain Tumor Progress Review Group identified many priorities for the field. Research on understanding and preventing brain tumor dispersal was one of the group's highest scientific priorities, and NIH funds a number of projects in this area, many of which were submitted in response to a Program Announcement with set-aside funds issued in 2004. 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.

- For more information, see http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm
- This example also appears in Chapter 2: *Cancer.*
- (E/I) (**NINDS**, NCI)

Know Stroke in the Community Educational Campaign: In 2004, NIH entered a first-time partnership with CDC to launch a new grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders, called "Stroke Champions," who worked to educate communities about the signs and symptoms of stroke. The program focuses on reaching African Americans, Hispanics, and seniors in communities that have the health care systems in place to treat stroke. In 2005-2006, the program had been implemented in 11 cities, educating 168 Stroke Champions who have conducted more than 600 community events.

- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E/I) (NINDS)

Peripheral Neuropathies: NIH funds studies focused on understanding the genetic basis and molecular and cellular mechanisms of many peripheral neuropathies, including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, inherited neuropathies such as Charcot-Marie-Tooth, inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy, and rare forms of peripheral neuropathy. In October 2006, NIH held a workshop that looked across different peripheral neuropathies to focus on steps needed for therapy development. The workshop brought together researchers in inherited and acquired peripheral neuropathies, representatives from voluntary disease groups, and NIH staff.

- (E) (NINDS, NIDDK)

Rare 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. New NIH-funded grants in FY 2006 and 2007 focused on rare diseases, such as Friedreich's ataxia, ALS, transmissible spongiform encephalopathies, and Rett syndrome. NINDS also collaborates with the Office of Rare Diseases (ORD) and patient voluntary organizations to stimulate research via workshops or grant solicitations. For example, lysosomal storage disorders, such as Fabry, Niemann-Pick, and Gaucher diseases, are rare genetic diseases with neurological manifestations. NINDS, ORD, and a patient voluntary group cosponsor an initiative to spur new research on the delivery of therapies for lysosomal storage disorders across the blood-brain barrier.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-06-202.html
- For more information, see http://www.ninds.nih.gov/about_ninds/plans/a-t_plan.htm
- (E) (**NINDS**, NCI, NCRR, NEI, NHGRI, NHLBI, NIA, NIAID, NICHD, NIDDK, NIEHS, NIGMS, ODP/ORD)

Translational Research: To meet the special needs of translational research across neurological disorders, NINDS has developed a program to support pilot projects, full-scale collaborative teams in academia and small businesses, and training efforts. Investigator-initiated proposals are rigorously peer reviewed, and expertise and criteria are tailored to translational research objectives. Funding is milestone driven, and the program fosters collaborative research. Ongoing projects are developing drug, stem cell, or gene therapies for ALS, Batten disease, epilepsy, Huntington's disease, Duchenne and other muscular dystrophies, Parkinson's disease, tuberous sclerosis, and stroke and other disorders. In 2008 the program will expand to include molecular diagnostics, which are critical for catching disease early, when intervention is most likely to succeed.

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

Acupuncture for Osteoarthritis of the Knee: Clinical trials supported by NIH and others suggest that acupuncture may have a useful role in treating a variety of chronic painful conditions, hypertension, and obesity. For example, in 2006 NIH-funded investigators reported findings from the longest, largest, randomized, controlled clinical trial of acupuncture ever conducted. The results demonstrated that acupuncture is an effective adjunct to conventional treatment for osteoarthritis, the most common form of arthritis and a major cause of pain, limitation of activity, and health care utilization among the elderly. Study participants receiving acupuncture had significantly reduced disability and improved quality of life. The innovative trial design resulted from an interdisciplinary collaboration of rheumatologists, licensed acupuncturists, and biostatisticians, ensuring that the research methodology was scientifically sound and accurately reflected acupuncture as traditionally practiced.

- Manheimer E, et al. *Acupunct Med* 2006;24:S7-14, PMID: 17308513

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (NCCAM)

How We Detect Taste at the Molecular Level: Taste is critical for discriminating between nutritious and spoiled foods. Taste disorders can lead to reduced appetite and poor nutrition. Scientists are trying to increase their understanding by identifying proteins that we produce to help detect taste. Taste cells are clustered in taste buds on the tongue and palate. NIH-supported scientists have identified a new protein, PKD1L3, found specifically in taste cells. The PKD1L3 protein forms a channel that allows tastants, such as sodium ions or protons, to enter through taste cell membranes so that tastes can be detected. Another group of NIH-supported scientists determined that the protein is located in taste pores and is activated by acids (sour) but not other tastants. A third group of NIH-supported scientists reports that mice lacking PKD2L1-expressing cells cannot detect sour tastants, but can detect all others. Together, these three reports suggest that PKD1L3 channels detect sour tastants in food. Scientists can now explain how humans detect the flavors sweet, sour, bitter, and umami, or savory, at the cellular level. This advance in understanding taste may help scientists treat taste impairments and could also lead to the development of better salt and sugar substitutes for the millions of Americans on restricted diets to control high blood pressure, diabetes, and obesity.

- Lopez-Jimenez ND, et al. *J Neurochem* 2006;98:68-77, PMID: 16891422
- Huang AL, et al. *Nature* 2006;442:934-8, PMID: 16929298
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E/I) (NIDCD)

Stuttering: Stuttering is a communication disorder with notable physical and emotional challenges to the speaker and sometimes to the listener. It is estimated that approximately 3 million Americans stutter. Stuttering affects individuals of all ages but occurs most frequently in young children between the ages of 2 and 6 who are developing speech and language. Boys are three times more likely to stutter than girls. Most children, however, outgrow their stuttering. It is estimated that less than 1 percent of adults stutter. NIH-supported scientists identified a specific location for a gene on chromosome 12 that seems to be an important contributor to stuttering in a series of 40 highly inbred families of Pakistani origin. Determining the underlying molecular causes of stuttering may lead to improved diagnosis and treatment.

- Riaz N, et al. *Am J Hum Genet* 2005;76:647-51, PMID: 15714404
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NIDCD)

Discovering the Molecular Mechanisms of Pain: Nociception, the sensory component of pain, depends in part on the intricate network of sensory transmission within our bodies, stretching from our extremities to the spinal cord and onward to the brain. But on its most fundamental level, nociception involves molecules and chemical mechanisms. NIH scientists have reported progress in understanding precisely how individual molecules in our nerve cells generate, transmit, and sustain sensory signals. They discovered that a much-studied protein called cyclin-dependent kinase 5 (Cdk5) plays a regulatory role in pain signaling between sensory nerves in the spinal cord and nerve ganglia. Their results offer the first direct evidence of this regulatory role for Cdk5. The authors also reported the first evidence from animal studies of the importance of Cdk5 activity in inflammation. These findings point the way for additional research, suggesting that new analgesic drugs that alter Cdk5 activity one day may be beneficial in treating pain.

- Pareek TK, Kulkarni AB. *Cell Cycle* 2006;5:585-8, PMID: 16552189
- Pareek TK, et al. *Proc Natl Acad Sci U S A* 2006;103:791-6, PMID: 16407116

- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (I) (NIDCR)

DNA Test for Charcot-Marie-Tooth Disease: Charcot-Marie-Tooth disease, one of the most common inherited neurological disorders, affects 1 in 2,500 people in the United States. Its symptoms start in early adulthood and include progressive arm and leg pain that leads to difficulty walking and manipulating objects. Using a special strain of mice, new genomic technologies, and information from the mouse and human genome sequences, NIH-funded researchers rapidly identified a mutation that causes a subtype of the disease. Knowledge of the specific gene defect will enable development of a DNA test to confirm the diagnosis in patients and predict risk for family members.

- Chow CY, et al. *Nature* 2007;448:68-72, PMID: 17572665
- For more information, see http://www.med.umich.edu/opm/newspage/2007/charcot.htm.
- This example also appears in Chapter 3: *Genomics.*
- (E) (**NIGMS**, NINDS)

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

National Institute of Neurological Disorders and Stroke (NINDS)

- *Neuroscience at the New Millennium*
- *Benchmarks for Epilepsy Research*
- *Report of the Stroke Progress Review Group*

National Eye Institute (NEI)

- *National Plan for Eye and Vision Research* (2004)
- *Vision Research–A National Plan 1999-2003: A Report of the National Eye Advisory Council*
- *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*

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*

National Institute of Mental Health (NIMH)

- *NIMH Strategic Plans and Priorities*
- *Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research*

- *Pathways to Health: Charting the Science of Brain, Mind, and Behavior*

National Institute on Drug Abuse (NIDA)

- NIDA Draft Strategic Plan

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

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

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 at NICHD*
- Branch Reports to Council with Future Research Directions:
    - National Center for Medical Rehabilitation Research NICHD, Report to the National Advisory Child Health and Human Development (NACHHD) Council, January 2006
    - *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* (Draft)

Office of AIDS Research (OAR)

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

Other Trans-NIH Plans

- *NIH Blueprint for Neuroscience Research*
  (NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, **NIMH, NINDS**, NINR, OBSSR)
- (NCCAM, NCRR, NHGRI, NIA, NICHD, NIDA, NIDCD, NIEHS, NIMH, **NINDS**, NINR)
- *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)
- The Autism Research Matrix
  (**NIMH**; NICHD; NIDCD; NINDS; NIEHS; CDC; ACF; HRSA; CMMS; SAMHSA; NIDDK)
- *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)

Summary of Research Activities by Disease Categories

Infectious Diseases and Biodefense

By 1986, there were 5,833 reported AIDS cases in the United States and the 1-year mortality was 51 percent. Efforts were being made to find something—anything—that would slow disease progression. A seminal discovery, made in 1970, was that an enzyme called reverse transcriptase was necessary for retroviruses like HIV to replicate. Based on this understanding, scientists began to screen existing agents to find candidate drugs that inhibited the enzyme. Drs. Robert Yarchoan, Hiroaki Mitsuya, and Samuel Broder found that zidovudine (AZT) had this property. AZT was then quickly placed in a placebo-controlled clinical trial in patients with late-stage disease. The first review of data in September 1986 showed 19 deaths in the placebo group compared with 1 death in the AZT treatment group. The study was stopped and the FDA approved the drug in record time. It was 21 months from trial initiation to drug approval—an FDA record that has never been surpassed.

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 nonserious to life-threatening and can be transmitted in many ways. Influenza and 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, during sexual intercourse, and from mother to child at birth or during breast-feeding; and malaria is caused by a microscopic parasite that is transmitted by an insect “vector,” in this case a mosquito. Unlike chronic and degenerative illnesses, transmissible infectious diseases can rapidly devastate large human populations and easily cross international borders

Biodefense and Emerging and Reemerging 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. The NIH biodefense strategy is designed to protect all civilian populations and integrates basic, applied, and clinical research knowledge and capabilities into a flexible and adaptable “network.” Other threats to public health change continually as new pathogens emerge and as familiar microbes reemerge with new properties or in unusual settings. Examples of recent emerging and reemerging public health threats include naturally occurring infectious diseases such as Ebola hemorrhagic fever and severe acute respiratory syndrome (SARS). The overall goal of research on biodefense and emerging and reemerging 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, NINDS, and the NIH Office of AIDS Research (OAR). Nearly every NIH IC supports AIDS-related research activities, consistent with their individual missions. The ICs that conduct most of the research on AIDS and related co-infections, malignancies, cardiovascular and metabolic complications, and behavioral and social science issues are NIAID, NIDA, NCI, NIMH, the National Center for Research Resources (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). 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 could be misused to pose a threat to public health or national security—taking into consideration both national security concerns and the needs of the research community.

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 new 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 are inherently 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 low- and middle-income countries. Within the United States, NIH seeks strategic partnerships with other governmental and nongovernmental organizations.

NIH supports research on HIV/AIDS, TB, malaria, emerging and reemerging 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[24].

NIH research on biodefense and emerging and reemerging infectious diseases is necessarily 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; and the targeted development of medical countermeasures, including vaccines, therapeutics, and diagnostics that would be needed in the event of a biological, chemical, or radiological weapons attack.

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 occurring 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. HIV causes nearly 2.1 million total deaths each year[25], TB kills 1.6 million each year, and

[24] For more information, see http://www3.niaid.nih.gov/Biodefense

[25] For more information, see http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate?epiUpdArchive/2007default.asp

lower respiratory infections in 2005 caused an estimated 3.7 million deaths[26]. Malaria is a serious problem, especially in Africa, where one in every five childhood deaths is due to the effects of the disease[27]. 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[28].

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[29].

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[30].

In the United States, infectious diseases add significantly to the overall burden of illness. Together, influenza and pneumonia account for more than 60,000 deaths annually[31]. More than a million cases of sexually transmitted diseases occur each year, and more than 42,000 new cases of AIDS were reported in 2004[32].

Also, many infectious diseases are increasingly 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 Disease and Biodefense Research

FYs 2006 and 2007, NIH funding for infectious diseases research was $3.132 billion and $3.059 billion respectively. Funding for biodefense research was $1.766 billion and $1.735 billion. There is substantial overlap in these funding figures. The table at the end of this chapter indicates some of the research areas involved in this investment (see "Estimates of Funding for Various Diseases, Conditions, and Research Areas").

Summary of NIH Activities

[26] For more information, see http://www.dcp2.org/main/Home.html; http://www.who.int/entity/mediacentre/factsheets/fs310.pdf

[27] For more information, see http://www.who.int/features/factfiles/malaria/en/index.html

[28] For more information, see http://www.dcp2.org/pubs/GBD/3/Table/3.14

[29] For more information, see http://www.dcp2.org/main/Home.html

[30] For more information, see http://www.dcp2.org/main/Home.html

[31] For more information, see http://www.cdc.gov/nchs/fastats/deaths.htm.

[32] For more information, see http://www.cdc.gov/nchs/fastats/infectis.htm

NIH programs on infectious diseases and biodefense encompass a broad range of basic, translational, preclinical, and clinical research. These activities include developing critical research resources and infrastructure domestically and abroad that allow NIH to respond effectively to existing and emerging infectious diseases wherever they occur.

Basic Research

Basic research on infectious diseases and biodefense seeks to increase understanding of how pathogens cause disease and how hosts respond to infection; it provides the foundation for improvements in the prevention, diagnosis, and treatment of infectious diseases. For example, NIH researchers recently discovered how a surface protein of the virus that causes chicken pox and shingles attaches to a host cellular protein. That finding, in turn, has opened the door to designing and developing new treatments that block the virus-attachment process.

Many challenges remain in basic research on infectious diseases. These include further definition of the mechanisms by which the immune system protects against infection and of the intricate interactions that occur between pathogens and their hosts; more precise identification of the driving forces behind changing global patterns of infectious diseases; uncovering additional links between infectious diseases (and the immune responses to them) and the development of some cancers, as well as some autoimmune, cardiovascular, and neurological disorders; and discovering how and why genetic changes arise that make pathogens more dangerous. For example, HIV, H5N1 influenza, and Ebola virus originated in animals but mutated and acquired the ability to infect humans. Also, microbes that cause TB, AIDS, and influenza are mutating and acquiring resistance to antimicrobial drugs, which has prompted NIH to develop research initiatives and programs to expand investigations of the basis of antimicrobial resistance, including how bacteria develop and share resistance genes.

Many advances in understanding infectious diseases are the result of the revolution in genomic sequencing that has occurred in the past decade. In FYs 2006 and 2007, NIH-funded researchers and their collaborators completed a range of genome-sequencing projects that help reveal how microbes evolve, infect host cells, cause disease, develop drug resistance, and spread. The studies include sequencing the complete or partial genomes of 54 different samples of the malaria parasite, *Plasmodium falciparum*; a common sexually transmitted parasite, *Trichomonas vaginalis*; an oral bacterium; and more than 2,800 samples of avian and human influenza viruses[33]. Several of the genome-wide association studies funded by NIH examine genetic variations and explore susceptibility to infection or responses to smallpox, anthrax, typhoid, and cholera vaccinations (see also the section "Genomics" in Chapter 3).

Major Infectious Diseases

NIH conducts research on hundreds of infectious diseases, placing special emphasis on those that claim large numbers of lives each year and cause widespread suffering. NIH also explores how human behaviors as well as social, cultural, economic, and geographic factors affect disease transmission. Additionally, NIH conducts studies to evaluate and ensure the health of special populations, including minorities, individuals who are immunocompromised, the elderly, adolescents, young children, and infants. The ultimate goal is to translate knowledge gained through basic research into interventions that improve public health.

Tuberculosis

TB is an old disease but still ranks high among the foremost microbial killers of the 21st century and is particularly common among people with HIV. NIH supports a large portfolio of research to develop new drugs, vaccines, and diagnostics for TB and to evaluate improved treatment and prevention regimens. New drugs currently in clinical

[33] For more information, see http://www.niaid.nih.gov/dmid/genomes/mscs/influenza.htm

trials include SQ-109, a promising candidate therapy being developed in a private-public partnership. After a hiatus of 60 years in which no new TB vaccines were clinically tested, at least 9 candidates are now in human trials and at least 10 more are in preclinical development.

The rapid emergence of drug-resistant forms of TB poses an increasing and dangerous public health threat. Both MDR-TB and XDR-TB are classified as emerging infectious diseases and are increasingly difficult to treat. NIH supports the development of new and improved diagnostic tools to more accurately diagnose early TB disease, help optimize therapy by identifying drug-resistant strains, and track the spread of TB in communities. To ensure that research continues to contribute effectively to the global response to the increasing TB threat, in 2007 NIH developed a comprehensive TB research agenda. The plan incorporates NIH collaborations with other U.S. Government agencies and multilateral organizations worldwide and supports public-private partnerships to benefit people who have TB, including individuals who are co-infected with HIV.

Malaria

The age-old scourge of malaria claims millions of lives every year, mostly among children. The broad NIH malaria research portfolio and the malaria research agenda currently under development are designed to improve understanding of malaria parasites, host responses, and vector biology, thereby accelerating the development of new and improved public health interventions, including vaccines, therapeutics, and vector management. NIH is collaborating with strategic partners to develop vaccines for malaria and is currently testing several candidate vaccines in malaria-endemic areas. In 2007, NIAID began a new initiative entitled "NIAID Partnerships with Public-Private Partnerships." This initiative seeks to support the role of public-private partnerships in the development of new drugs, vaccines, and diagnostics for diseases such as malaria, trypanosomiasis, leishmaniasis, and other neglected tropical diseases.

HIV/AIDS

In the countries hardest hit by HIV/AIDS, the disease has lowered life expectancy, orphaned millions of children, lowered family income, reduced worker productivity, and diminished the supply of teachers and health care workers[34]. NIH plays many critical roles in the global effort to conquer HIV. Antiretroviral therapies made possible by NIH-supported research have resulted in improved quality of life and life expectancy for people who have access to these drugs. A recent study concluded that, since 1996, these antiretroviral medications have saved at least 3 million years of life in the United States alone. Worldwide, more than 2 million people receive antiretroviral therapy, more than half of them with support from the President's Emergency Plan for AIDS Relief (PEPFAR). However, the use of these antiretroviral therapies is associated with a range of side effects and long-term complications that may have a negative impact on mortality rates. The appearance of multidrug-resistant strains of HIV presents an additional serious public health concern. NIH AIDS research programs are addressing these and other complications.

The broad effort to extend the availability and use of anti-HIV drugs to regions most affected by HIV/AIDS continues. NIH is funding research to develop therapeutic regimens that are easier to use in resource-limited settings, as well as new antiretroviral drugs that target HIV in novel ways. In one of the largest HIV/AIDS treatment trials ever conducted, NIH-funded scientists participating in an international collaboration involving 318 clinical sites in 33 countries showed that HIV-positive individuals who receive episodic treatment with anti-HIV drugs have twice the risk of disease progression, including death from AIDS, than do those who receive continuous therapy with antiretroviral drugs. In addition, the recently Children with HIV Early Antiretroviral Therapy study in South Africa showed that treating HIV-infected children early with antiretroviral drugs helps them live longer.

[34] For more information, see http://www.kff.org/hivaids/7661.cfm

Another key research priority is prevention and treatment of HIV-associated co-infections, such as TB and hepatitis C, and comorbidities, such as HIV-associated malignancies, cardiovascular disease, and neurological complications. Studies are evaluating the incidence and treatment of metabolic and cardiovascular disease in people who receive long-term antiretroviral therapy. In addition, the AIDS Malignancy Consortium has launched several clinical studies to identify appropriate treatment regimens for HIV-infected individuals with cancer.

Successful efforts to prevent the spread of HIV and improve adherence and access to treatment are also driven by research in behavioral and social sciences that extends understanding of decision-making, drug abuse, and sexual behavior. As people changed risky behaviors, new AIDS cases in the United States were nearly halved from a peak of over 80,000/year in 1993[35], to 42,000/year in 2005[36]. Previously 1,650 babies were born infected with HIV each year but today that number is less than 50[37]. Whether preventing transmission, engendering trust to encourage testing and early treatment, or increasing adherence and access to the latest medications and health services, slowing the spread of HIVAIDS involves understanding (basic behavioral and social science) and changing human behavior at individual, group and community levels.

NIH continues to place a high priority on HIV prevention research, including research to develop vaccines, microbicides, strategies to prevent mother-to-child transmission, antiretroviral therapy as a pre-exposure prophylaxis strategy, treatment for drug addiction, and behavioral interventions. NIH-sponsored studies recently demonstrated that the use of antiretroviral prophylaxis can reduce the rate of mother-to-child transmission of HIV from approximately 25 percent to less than 2 percent. NIH also supports research to develop and test other prevention strategies, such as circumcision. For example, NIH-supported clinical trials in Kenya and Uganda showed that medically supervised circumcision of adult males can significantly lower their risk of contracting HIV through heterosexual intercourse by approximately 50 percent. In countries hit hard by HIV, adult male circumcision serves as another prevention strategy that could result in fewer HIV infections.

Topically applied microbicides for women and men are another promising avenue for preventing HIV transmission. Several microbicides have entered large-scale efficacy trials, the results of which are expected in the next few years. In 2006, NIH established the Microbicide Trials Network to develop safe and effective microbicides to prevent HIV transmission. In addition to basic and clinical research, studies of cultural and behavioral factors related to acceptability and adherence of prevention interventions are under way.

The ultimate prevention tool, and what is considered the best hope to end the HIV/AIDS pandemic, is a safe and effective vaccine that could prevent HIV infection. NIH-supported researchers around the world have developed candidate vaccines against HIV, some of which are now being tested in various phases of clinical trials. One example is the large-efficacy HIV vaccine trial in Thailand that is being conducted with support from NIH. The NIH Vaccine Research Center, as well as the NIH-supported HIV Vaccine Trials Network, is also dedicated to developing and testing new HIV vaccine candidates, including some that target different HIV types (called clades). To overcome key scientific roadblocks to HIV vaccine development and facilitate the design and testing of HIV vaccine candidates, NIH established the Center for HIV/AIDS Vaccine Immunology, an international consortium of

[35] For more information, see http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2004report/pdf/2004SurveillanceReport.pdf

[36] For more information, see http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2005report/

[37] For more information, see http://www.cdc.gov/hiv/topics/perinatal/resources/factsheets/perinatal.htm

scientists. NIH is a member of the Partnership for AIDS Vaccine Evaluation, a consortium of U.S. Government agencies and key U.S. Government-funded organizations involved in the development and evaluation of HIV vaccines. NIH also recently reissued a notice of program project awards for the HIV Vaccine Research and Design Program, which supports multiproject, multidisciplinary HIV/AIDS vaccine-related studies.

Emerging Infectious Diseases and Biodefense

NIH has mounted a comprehensive and vigorous research program to address critical challenges posed by naturally emerging and reemerging infectious diseases, as well as to mitigate the threats of biological, chemical, or nuclear/radiological terrorism. The goals of these overlapping programs are to develop the capacity to respond rapidly to public health threats; better understand the patterns and means by which pathogens spread and how they cause disease; decipher the mechanisms by which pathogens that infect animals mutate and acquire the ability to infect humans; and develop safe and effective medical countermeasures against naturally occurring, accidental, and deliberately introduced public health threats.

Influenza is a classic example of a reemerging infectious disease. The influenza viruses that caused the pandemic World War I-era Spanish flu and the current avian flu (caused by the H5N1 influenza virus) began in birds, mutated and spread to mammals (pigs, cats, etc.), and then mutated further and acquired the ability to infect humans. Thus, the spread of H5N1 from birds to humans underscores the urgent need to develop better vaccines and drugs to protect against pandemic influenza, as well as the seasonal epidemics that claim an average of 36,000 lives per year in the United States alone.

In 2006, NIH undertook a comprehensive examination of its influenza portfolio and convened a Blue Ribbon Panel on Influenza Research to identify areas of influenza research in which progress is needed. To help implement the panel's recommendations and facilitate a broad spectrum of influenza research, NIH has adopted several strategies. In 2007, NIH made multiple awards to support innovative influenza research to advance the development of promising vaccines, adjuvants, therapeutics, immunotherapeutics, and diagnostics. NIH also established six Centers of Excellence for Influenza Research and Surveillance to expand its ability to conduct research on different strains of animal and human influenza viruses collected in other countries or the United States. NIH researchers are collaborating extensively with other Department of Health and Human Services (HHS) agencies, across other Federal agencies, with private industry, and internationally and are working with strategic partners to develop DNA-, recombinant virus-, and recombinant protein-based candidate influenza vaccines. NIH also leads an international collaborative effort to analyze national and global epidemiological patterns associated with influenza virus circulation.

To date, NIH research has laid the foundation for improved influenza vaccine manufacturing methods, new categories of vaccines that may work against multiple influenza strains, and the next generation of anti-influenza drugs. The inactivated-virus H5N1 vaccine currently stockpiled by HHS has been shown in NIH-sponsored clinical trials to be safe and capable of inducing an immune response predictive of being protective against the H5N1 virus in healthy adults, children, and seniors.

To date, NIH research has laid the foundation for improved influenza vaccine manufacturing methods, new categories of vaccines that may work against multiple influenza strains, and the next generation of anti-influenza drugs. The inactivated-virus H5N1 vaccine currently stockpiled by HHS has been shown in NIH-sponsored clinical trials to be safe and capable of inducing an immune response predictive of being protective against the H5N1 virus in healthy adults, children, and seniors.

Biological Countermeasures Research

NIH supports research on a range of emerging and reemerging pathogens that are also considered potential agents of bioterrorism, including Marburg and Ebola hemorrhagic fever viruses, smallpox, and anthrax. NIH-supported researchers are probing the ecology of how these infections arise, identifying the natural hosts and modes of natural transmission of pathogens and developing safe and effective vaccines and treatments. For example, NIH-funded scientists recently developed promising candidate vaccines for Ebola and Marburg hemorrhagic fever viruses. The Marburg vaccine has been tested in rhesus monkeys and helped all of them survive a later challenge with live virus. An experimental Ebola vaccine has entered human clinical trials.

Chemical Countermeasures

Within HHS, NIH is leading the development of new and improved medical countermeasures designed to prevent, diagnose, and treat the conditions caused by chemical agents that could be released either accidentally or deliberately. To guide this research, NIH has prepared the "Strategic Plan and Research Agenda on Medical Countermeasures Against Chemical Threats." Under this plan and in collaboration with DoD, NIH has established the trans-agency CounterACT Research Network. The network has established four Centers of Excellence in Medical Chemical Research; funded more than two dozen research projects focusing on nerve agents, sulfur mustard and other blister-causing agents, cyanide and other metabolic poisons, and pulmonary agents; and awarded several Small Business Innovation Research grants for therapeutics and diagnostics development.

Nuclear/Radiological Countermeasures

To enhance readiness in the event of a radiological or nuclear threat, NIH has developed a strategic plan and research agenda. To help implement the plan, NIH has issued an RFA to conduct research to validate existing biodosimetry tools that evaluate radiation doses to which individuals have been exposed and to develop new biodosimetry assays and tools. NIH also issued RFAs to support the research and development of medical countermeasures to enhance survival after radiation exposure.

NIH works closely with HHS to periodically update and prioritize the research development activities of its strategic plan and ensure its integration as a key component of the larger national biodefense research agenda. The Radiation Event Medical Management Program (REMM) provides online guidance to health care providers about diagnosis and treatment for radiation-induced injuries. Further, in collaboration with the HHS Office of the Assistant Secretary for Preparedness and Response, NIH has prepared a downloadable, online diagnostic and treatment tool kit to guide health care providers during a mass casualty radiation event.

Infrastructure and Research Resources

NIH continues to develop the infrastructure necessary to carry out pioneering research on infectious diseases. As research capabilities (e.g., genomics, proteomics, microarray technology) have evolved and research needs have changed, new facilities and research resources have been designed, implemented, and enhanced. However, since the U.S. anthrax attacks of 2001, the emergence of severe acute respiratory syndrome (SARS) in southeast Asia, repeated outbreaks of hemorrhagic fever viruses in Africa, the threat of pandemic influenza, and other actual and potential public health emergencies, there is an increased need to develop the ability to respond rapidly to public health threats. To this end, NIH has established or expanded reagent and tissue repositories, data centers, and centralized analytical laboratories and is expanding the number of extramural research facilities nationwide. The latter include the 6 Centers of Excellence for Influenza Research and Surveillance mentioned above, 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, 2 National Biocontainment Laboratories (with BSL-4 capacity, the highest level of containment), 13 Regional Biocontainment Laboratories with BSL-3 capacity, 8 Human Immunology Centers, 10 centers to study host immunity in special populations (children, pregnant women, elderly, immunosuppressed individuals), clinical trials networks at domestic and international sites, and nonhuman primate research centers. In addition, three intramural biocontainment laboratories—on the

NIH campus in Bethesda, Maryland (BLS-3); on the National Interagency Biodefense Campus at Fort Detrick in Frederick, Maryland (BSL-4); and at the NIAID Rocky Mountain Laboratories in Hamilton, Montana (BSL-4)—are operational or nearing completion.

International Collaboration

Much of NIH infectious disease and biodefense research is collaborative, interdisciplinary, and—increasingly—international. NIH supports research and training programs to develop and test safe and effective interventions for preventing and treating infectious diseases, exchanging scientific information, and building research capacity in other countries (see also the section "Research Training and Career Development" in Chapter 3). These efforts include programs to establish research resources and infrastructure, for example, to help train scientists from developing countries to engage in infectious disease research, including clinical, operational, and health services research, and to help establish sustainable research capacity in those countries. Because HIV/AIDS and TB take such an enormous global toll, NIH is strengthening the capacity for clinical, operational, and health services research in low- and middle-income countries where HIV/AIDS, TB, or both are significant problems. NIH has established critical global partnerships with the World Health Organization and other United Nations agencies, governmental and nongovernmental organizations, international foundations, and private-sector organizations. Additionally, NIH is establishing international collaborations to develop a safe, effective vaccine against malaria and to gather and analyze national and global epidemiological patterns associated with influenza virus circulation, including data on mortality, virus surveillance, genomics, and control strategies.

Notable Examples of NIH Activity

Key for Bulleted Items:

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, and communication)
COE = Supported through a congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = Concerns progress tracked under the **G**overnment **P**erformance and **R**esults **A**ct

Basic Research

Microbial Genomics: NIH has made significant investments in large-scale, whole-genome sequencing of pathogens over the last decade. Sequenced pathogens include hundreds of bacteria, fungi, parasites, invertebrate vectors of diseases, and viruses (including the pathogens that cause anthrax, influenza, aspergillosis, TB, gonorrhea, chlamydia, and cholera and many that are potential agents of bioterrorism). NIH also provides comprehensive genomic, bioinformatic, and proteomic resources and reagents to the scientific community. These include the (1) Microbial Genome Sequencing Centers, which rapidly produce high-quality genome sequences of human pathogens and invertebrate vectors of diseases; (2) Pathogen Functional Genomics Resource Center, which provides functional genomic resources; (3) Bioinformatics Resource Centers, which provide access to genomic and related data in a user-friendly format; and (4) Proteomics Research Centers, which support research on the full set of proteins encoded in a microbial genome. The NIH Influenza Genome Sequencing Project has sequenced more than 2,800 human and avian isolates (as of November 28, 2007); NIH scientists recently exploited these data to explain the global spread of resistance to adamantanes, a first-generation class of anti-influenza drug.

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

Scientists Complete Full Sequence of Opportunistic Oral Bacterium: Over the last decade, scientists have assembled the complete DNA sequences of several important oral bacteria. Now NIH-funded investigators have decoded and added another important bacterium, *Streptococcus sanguinis*, a key player in the formation of the oral biofilm, to the list. Although not regarded as a pathogen in the mouth, S. *sanguinis* is known to enter the bloodstream, where it can colonize heart valves and contribute to bacterial endocarditis, a condition that kills an estimated 2,000 Americans each year. With the bacterium's genetic blueprint now publicly available online, scientists can better study the dynamics of biofilm formation and possibly tease out new leads to prevent tooth decay and periodontal disease. They can also now systematically identify and target sequences within the DNA of S. *sanguinis* that are critical to the infectious process, invaluable information in designing more effective treatments for endocarditis.

- Xu P, et al. *J Bacteriol* 2007;189: 3166-75, PMID: 17277061
- This example also appears in Chapter 3: *Genomics*.
- (E) (NIDCR)

Major Infectious Diseases

Malaria Vaccine Research: Malaria continues to be one of the most devastating diseases throughout the world today. The number of cases of the disease ranges from 350 million to 500 million each year, resulting in more than 1.1 million deaths, primarily among young children in Africa (World Health Organization [WHO]). To address this important public health issue, the WHO Initiative for Vaccine Research reports that, as of August 2005, there are at least 45 candidate vaccines in preclinical development and 26 in clinical trials. NIH plays a valuable role in funding a number of these activities, supporting 15 of the candidates in preclinical development and 5 of the candidates in clinical trials. Examples of NIH-supported activities include the following:

- NIH researchers have applied an innovative technology, tested in mice, that may prompt an individual's immune system to eliminate the malaria parasite from the mosquito. Because the vaccine targets the parasite instead of conferring protection to the individual, it has the potential to eradicate malaria from large geographic regions.

- NIAID, in collaboration with the Walter Reed Army Institute of Research, GlaxoSmithKline Biologicals, the U.S. Agency for International Development, and others, has completed a Phase I adult trial in Mali of a novel candidate vaccine that works by blocking the replication of malaria parasites in the blood. Additional studies in children (who have the highest death toll among malaria cases) are under way.

  - For more information, see http://www.who.int/vaccine_research/diseases/soa_parasitic/en/index4.html
  - (I) (NIAID, NICHD, NIDDK)

Value of Early HIV Screening, Testing, and Counseling: HIV/AIDS disproportionately affects several minority groups, particularly African Americans. Although adult and adolescent African Americans make up approximately 13 percent of the population, they accounted for half of the new HIV/AIDS diagnoses in 2001-2005. This disparity is particularly striking because African Americans do not have higher rates of addiction or intravenous drug use than Whites. One contributing factor is that African Americans are often diagnosed with HIV infection at a later point in

the illness, increasing their likelihood of progressing to AIDS and of transmitting the disease. As part of efforts to 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 links among education, testing and counseling, and treatment within all ethnic groups. Indeed, 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. The CDC has recognized that these findings have important public health implications and 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/ResearchReports/hiv/hiv.html
- For more information, see http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm.
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIDA)

Special Journal Issue: "Cultural Dynamics in HIV Prevention Among Young People": Twenty-five years of behavioral and biomedical research have led to breakthroughs in the prevention and treatment of HIV disease; however, young people have not fully benefited from these advances. In September 2005, NIH held a workshop, "Cultural Dynamics in HIV/AIDS Biobehavioral Research Among Young People." In March 2007, a special issue of the *Journal of the Association of Nurses in AIDS* Care presented a series of papers developed from this workshop. These papers are focused on current research into preventing the spread of HIV infection among youths from many cultures across the United States and around the world.

- Hare ML, Villarruel AM. *J Assoc Nurses AIDS Care* 2007;18:1-4, PMID: 17403490
- For more information, see http://www.ninr.nih.gov/NewsAndInformation/JANAC/
- (E) (NINR)

Adolescent Medicine Trials Network for HIV/AIDS Interventions (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 impact the transmission dynamics 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 youth and those at risk of infection. Researchers in this network are building the capacity to develop and conduct selected biomedical, behavioral, and community-based studies, including vaccine and microbicide trials to ensure that the needs of high-risk teens (e.g., alcohol- or drug-abusing adolescents) have access to the most promising treatment and prevention interventions as they are being developed.

- 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)

Diagnosis of Malaria by Microscopy: Virtually all clinical decisions, epidemiological surveys, field trials of drugs and vaccines, and evaluations of intervention programs in malaria depend on diagnoses made by microscopy. NIH has undertaken the first systematic analysis of errors and sources of error in malaria microscopy. This multiyear study includes the best malaria clinics in the tropical world and found 13 percent false-negative and 24 percent false-positive rates. Follow-up work is analyzing the accuracy and effect of different microscopy techniques, using different blood samples from the same patient, different microscope slides from the same blood sample, aspects

of parasite and patient biology, microscopist training, and other factors.

- O'Meara WP, et al. *Malaria J* 2006;5:118, PMID: 17164007
- (O) (FIC)

Microbicides: With more than 19.2 million women worldwide living with HIV/AIDS and more than 80 percent of HIV infections spread through heterosexual activity, NIH collaborative research is developing new ways to help women protect themselves from the virus. This includes the development and testing of agents that, if applied topically to genital areas, inactivate the virus or otherwise prevent susceptible cells from being infected with HIV. Scientists are working to develop, standardize, and validate innovative ways to rapidly screen large numbers of potential antimicrobial agents for irritation and safety. In addition, work is under way to examine the behavioral and social factors influencing whether individuals or couples would adopt and use new antimicrobial products consistently and effectively.

- (E) (NICHD, NIAID)

Culturally Appropriate Research to Prevent HIV Infection: Great strides have been made in the past 25 years in treatment and prevention strategies to combat the spread of HIV/AIDS in the United States. However, many populations in the United States and around the world have not benefited from these developments, and this is especially true for young people. One possible reason for such disparities is the influence of cultural differences on the effectiveness of prevention and treatment strategies. In fall 2006, NIH solicited proposals for innovative research to design and test interventions to prevent HIV transmission among young people. Areas of research interest include developing prevention/treatment interventions for young people with HIV/AIDS that take into account the cultural differences of those infected, determining the influence of cultural differences on how young people view living with HIV/AIDS and how these differences affect their views on preventing the spread of the disease, and examining challenges in transferring successful interventions across cultures, especially to other parts of the world.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-003.html
- (E) (NINR)

The Program in HIV/AIDS < Cancer Virology: The mission of this program is to facilitate and rapidly communicate advances in the discovery, development, and delivery of antiviral and immunologic approaches for the prevention and treatment of HIV infection, AIDS-related malignancies, and cancer-associated viral diseases. This includes basic laboratory, translational, and clinical studies of disease pathogenesis and the development of novel targeted treatment approaches for cancers in HIV-infected individuals, as well as HIV infection itself, and drug resistance. Recent advances include a new prophylactic vaccine for HPV and promising candidates for prophylactic and therapeutic vaccines for HIV.

- For more information, see http://ccr.nci.nih.gov
- This example also appears in Chapter 2: *Cancer*.
- (E/I) (NCI)

The NCI Vaccine Program: NCI's vaccine program develops novel vaccines for cancer immunotherapy and prevention and HIV. The program encourages collaborations, identifies organizational and reagent needs for the community, and develops the optimal infrastructure for vaccine development and novel clinical trial approaches. Gardasil®, the first vaccine to prevent cervical cancer induced by HPV, is now available and can potentially save

more than 5,000 U.S. women's lives each year. This FDA-approved vaccine resulted from the basic research performed at NIH that produced a prototype vaccine and the observation that linked HPV and cervical cancer.

- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research*
- (E/I) (NCI)

Retrovirus Epidemiology Donor Study (REDS): REDS was begun by NIH in 1989 to determine the prevalence and incidence of HIV infection among blood donors and the risks of transmitting HIV and other viruses via transfusions. In 2004, NIH launched REDS-II to monitor the appearance of newly discovered infectious agents in the blood supply, evaluate the characteristics and behaviors of voluntary blood donors, determine the causes of transfusion reactions of unknown etiology, assess the results of new donor screening methods, assess the effects of new blood-banking technologies, and evaluate the donation process. In 2005, an international component was added to REDS-II to conduct research on blood donors in selected countries seriously affected by the AIDS epidemic to ensure the safety and availability of blood for transfusion.

- For more information, see http://clinicaltrials.gov/ct/show/NCT00097006;jsessionid=7A9763F65A8C734DA771CDB5210D4877?order=7
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NHLBI)

Improved Management of Antiretroviral Therapy for Adults and Children: Two recent NIH studies transformed the management of antiretroviral therapy by extending the survival of adults and children with HIV/AIDS. Results from the Strategies for Management of Antiretroviral Therapy (SMART) study, one of the largest HIV/AIDS treatment trials ever conducted, showed that episodic use of antiretroviral therapy based on CD4+ cell levels is inferior to the use of continuous therapy for treatment-experienced patients and that deliberately interrupting antiretroviral therapy more than doubles the risk of developing AIDS or dying from any cause. The Children with HIV Early Antiretroviral Therapy (CHER) Study examined early antiretroviral therapy in South African children. Interim data showed a 96 percent increase in survival among infants who received immediate antiretroviral therapy compared with infants who received therapy later.

- SMART Study Group et al. *N Engl J Med* 2006;355:2283-96, PMID: 17135583
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2006/smart06.htm
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NIAID)

New Approaches to Diagnostics: Recognizing the urgent need for rapid, highly sensitive, and specific clinical diagnostics that can diagnose individuals exposed to or infected by human pathogens, NIH has developed a comprehensive research program that is taking advantage of genomic information and emerging technologies, such as nanotechnology, to develop new and improved diagnostic tools. The program covers a broad range of activities, including the development of improved sample preparation and processing, platform development, enhanced detection methods, and clinical validation. Program priorities include development of tools that can distinguish between a variety of pathogens or that can determine pathogen subtypes and their sensitivity to drug treatments.

- (E) (NIAID)

NIAID HIV Vaccine Research Education Initiative (NHVREI): This new national initiative is designed to educate the

public about HIV vaccine research, especially at-risk populations such as African Americans, Hispanics, men who have sex with men, and women at high risk of HIV infection. The goal is to increase awareness about the urgent need for an HIV vaccine within the communities that are most affected by HIV/AIDS, create a supportive environment for current and future volunteers in HIV vaccine trials, and improve the public's perceptions and attitudes toward HIV vaccine research. The NHVREI Local Partnership Program provides support to partner organizations in targeted communities to help achieve the initiative's goals.

- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2006/bethegeneration.htm
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NIAID)

Research Agenda for MDR-TB/XDR-TB: Diagnosing, treating, and controlling the spread of TB has become increasingly complicated by the HIV/AIDS co-epidemic and the emergence of MDR-TB and XDR-TB, which together threaten to set TB control efforts back to the pre-antibiotic era. In response to this urgent situation, in June 2007, NIH released its research agenda, *Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis*. The research priorities identified in the agenda build on a foundation of ongoing NIH-supported TB research, which currently comprises more than 300 research projects worldwide. This Web-based "living document," identified as such because of NIH's ability to modify, amend, or update it as scientific and public health needs and opportunities evolve, was prepared in close collaboration with other Government and non-Government organizations and reviewed by TB specialists in academia, advocacy groups, international organizations, and other Government agencies. It identifies 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, and (6) TB prevention, including vaccines.

- For more information, see http://www3.niaid.nih.gov/topics/tuberculosis
- (E/I) (NIAID)

The Evolving HIV Epidemic: Beyond Intravenous Drug Use: The nature of the HIV epidemic in this country is changing. Effective medications and HIV risk reduction interventions in intravenous drug abusers have helped to curb the spread of HIV though injection drug use to a point where it now accounts for a smaller percentage of new infections. However, drug abuse continues to play a major role in the spread of HIV through other mechanisms: drug abusers proffer sexual behaviors to obtain drugs or money to support their addiction, and drugs of abuse can worsen the course of the illness and produce intoxication, which can alter judgment and decision-making and lead to impulsive and risky sexual behaviors. Recognition of this link is critical for developing more integrated and effective prevention strategies. A critical aspect of this message is that treatment of drug abuse is HIV prevention, an idea being furthered by NIH in concert with other Federal agencies, such as CDC.

- For more information, see http://www.drugabuse.gov/ResearchReports/HIV/HIV.html
- (E) (NIDA)

Understanding Factors Affecting the Use of Microbicides: NIH is planning an initiative on research directed toward understanding the complex interplay among individual, dyadic, social, and other contextual factors that may influence the initiation and sustained use of microbicides that are proven to be efficacious in reducing the risk of acquiring or transmitting HIV. In addition, the initiative will address research on prevention strategies that incorporate the use of microbicides and on the development of behavioral and social tools to assess product acceptability, initiation, and sustained use in a manner that will directly inform microbicide product development

and improvement.

- (E) (NIMH)

OAR-Sponsored Initiatives Targeting Scientific Needs in AIDS Research: OAR, through its planning process, identifies scientific areas that require focused attention and facilitates innovative, cross-institute, multi-institute, multidisciplinary activities to address those needs. OAR fosters these efforts by designating resources to jump-start program areas through funds for grant supplements to the ICs, establishing working groups or committees, sponsoring workshops or conferences to highlight a particular research topic, and sponsoring reviews or evaluations of research program areas. Examples include a Microbicide Innovation Program to accelerate the discovery of single and/or combination microbicides against HIV and STDs and a Prevention Science Initiative to foster innovative research in HIV prevention. OAR also supports initiatives to enhance dissemination of research findings, including sponsorship of a group of scientific panels that develop AIDS treatment and prevention guidelines, and the distribution of those guidelines through *AIDSinfo*, a Web-based service to provide up-to-date information for caregivers and patients about AIDS treatment and prevention.

- For more information, see http://www.oar.nih.gov
- (O) (OAR)

Trans-NIH Management and Coordination of HIV/AIDS Research: NIH is the world's leader in AIDS research, representing the largest and most significant public investment in AIDS research in the world. Our response to the pandemic requires a unique and complex multi-institute, multidisciplinary, global research program. NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection and its associated co-infections, opportunistic infections, malignancies, and other complications. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every NIH IC. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds. OAR, located within the NIH Office of the Director, coordinates the scientific, budgetary, and policy elements of NIH AIDS research. Through its unique, trans-NIH planning, budgeting, and portfolio assessment processes, OAR ensures that AIDS research dollars are invested in the highest priority areas of scientific opportunity, allowing NIH to pursue a united research front against the pandemic.

- For more information, see http://www.oar.nih.gov
- (O) (OAR)

Development of New TB Diagnostic Tool: By detecting TB as early as possible, health providers can more effectively treat and control the disease in a population. An NIH-funded investigator working in Lima, Peru, has developed a new assay for TB. This simple and relatively inexpensive diagnostic test offers faster, more sensitive detection of TB and drug-resistant TB than the currently used method and cuts diagnostic time from an average of 28 days to 7 days. The new, inexpensive method is appropriate for countries with limited resources, and several countries are in the process of incorporating it into TB control protocols.

- Moore DA, et al. *N Engl J Med* 2006;355:1539-50, "PMID: 17035648
- (E) (FIC, NIAID)

Adult Male Circumcision Significantly Reduces Risk of Acquiring HIV: NIH-supported scientists announced an early end to two clinical trials of adult male circumcision because an interim review of trial data revealed that medically performed circumcision, with appropriate care in the postoperative period, significantly reduces a man's risk of

acquiring HIV through heterosexual intercourse. The trials, which enrolled 2,784 men in Kisumu, Kenya, and 4,996 men in Rakai, Uganda, showed that HIV acquisition in circumcised men relative to uncircumcised men was reduced by roughly half. Although the initial benefit will be fewer HIV infections in men, ultimately adult male circumcision could lead to fewer infections in women in those areas of the world where HIV is spread primarily through heterosexual intercourse. Circumcision remains only part of a broader HIV prevention research agenda that includes development of vaccines, microbicides, behavioral interventions, and prevention of mother-to-child transmission.

- Auvert B, et al. *PLoS Med* 2005;2:e298, PMID: 16231970
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2006/AMC12_06.htm
- (E) (NIAID)

Emerging Infectious Diseases and Biodefense

Biodefense Vaccines: NIH is the lead Federal agency within HHS for conducting research on potential agents of bioterrorism that directly affect human health. The terrorist attacks of September 11, 2001, and the deliberate exposure of civilians to anthrax spores prompted HHS to emphasize the importance of advancing vaccines for specific pathogens that could be used in bioterrorist attacks. In response, in February 2002, NIH convened the Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research. This panel was brought together to provide objective expertise on NIH's future biodefense research agenda in both the short and the long term. As expected, one of the identified areas of research emphasis was the development of new and improved vaccines against agents of bioterrorism, with the initial focus on smallpox and anthrax. Since that time, substantial progress has been made in biodefense vaccine research and development, which has resulted in the following advances:

- Modified Vaccinia Ankara, a new, safer smallpox vaccine that is the outcome of several years of NIH-sponsored research and development, has been purchased for the Strategic National Stockpile.
- An Ebola vaccine has been developed and is currently being tested in humans at NIH.
- A promising new anthrax vaccine candidate made with a purified protein has been developed and will enable researchers to determine the minimum level of protein needed to confer protection and minimize side effects.

- For more information, see http://www.hhs.gov/news/press/2007pres/06/pr20070604a.html
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2003/ebolahumantrial.htm
- (E/I) (NIAID, NICHD)

Microneedle-Based Immunization Against Pandemic Influenza: NIH is supporting a team of investigators under the Bioengineering Research Partnership grant mechanism to develop a low-cost, room temperature-stable, microneedle-based transdermal vaccine patch against pandemic influenza that could be rapidly distributed through pharmacies, fire stations, or the U.S. mail and painlessly self-administered. This dose-sparing delivery system will not produce any sharp, biohazardous waste and would avoid the expensive and time-consuming hypodermic vaccination process administered by medical personnel, thus allowing for a rapid response to pandemic influenza. This innovative application impacts the “HHS Pandemic Influenza Plan” and NIH's directives on high-priority influenza research areas.

- For more information, see http://www.hhs.gov/pandemicflu/plan
- This example also appears in Chapter 3: *Technology Development.*
- (E) (NIBIB)

Probes and Cell Arrays for Detection of Bacterial Toxins: Microarray technology offers an opportunity for

simultaneous monitoring the behavior of multiple markers within a mammalian cell and ultimately could be used for detection and elucidation of mechanisms of action of different biologically active agents, including those that are considered a threat in the biodefense area. The ultimate goal of this research project is to provide a general and robust approach for the detection of biologically active agents, especially when these agents have been engineered to elude currently available immunoassays. Cell arrays offer a new opportunity for sensitive and precise monitoring of biologically active substances. The goal of this project is to develop a system for the identification of regulatory elements that will allow a substantial extension of the discriminative abilities of cell arrays and the creation of cell arrays that are capable of detection and identification of potential biowarfare agents.

- (E) (NIEHS)

Antimicrobial Resistance Research: Antimicrobial resistance, which is caused by factors such as overuse of antibiotics, is severely jeopardizing the utility of many "first-line" antimicrobial agents and has emerged as a major public health threat. NIH supports a robust basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes. NIH is also pursuing translational and clinical research in this area, including clinical studies to test interventions for community-acquired MRSA infection, and to evaluate the efficacy of off-patent antimicrobial agents. NIH will continue to address high-priority research questions regarding resistance to help public health officials hold the line against drug-resistant microbes.

- For more information, see http://www.niaid.nih.gov/factsheets/antimicro.htm
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NIAID) (GPRA Goal)

Ecology of Infectious Diseases (EID): Jointly administered by NIH and the National Science Foundation (NSF), the EID program uniquely fills a critical gap in our national effort to protect public health against the threat of emerging infectious diseases. Most emerging diseases are initially transmitted from animals to humans, and some are capable of becoming pandemics. This program supports the discovery of the principles that govern the relationships between ecological disturbances and transmission of infectious agents, and the use of those principles to develop predictive models of epidemics. Potential benefits of the program include an increased capacity to forecast outbreaks and to improve understanding of how diseases emerge and reemerge.

- Eaton BT, et al. *Nat Rev Microbiol* 2006;4:23-35, PMID: 16357858
- For more information, see http://www.fic.nih.gov/programs/research_grants/ecology/index.htm
- (E) (FIC, NIAID, NIEHS)

Biodefense Therapeutics Development: Treatments 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 antimicrobial 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 therapeutics against diseases such as smallpox, botulism, and Ebola and West Nile virus infection. These projects range from preclinical services (such as performing medicinal and analytical chemistry, custom drug synthesis, formulation, clinical manufacturing, microbiology and virology screening, pharmacokinetics, and safety testing) to the development and testing of DAS 181 (Fludase),

which is potentially a broad-spectrum therapeutic agent for use against all annual and pandemic variations of influenza.

- For more information, see http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/research/funding/FY2006+Awards/therapeutic_awards.htm
- (E/I) (NIAID)

Developing New Adjuvants to Boost Vaccine Effectiveness: The NIH Innate Immune Receptors and Adjuvant Discovery initiative encourages the discovery of novel adjuvants to meet the growing need to boost the effectiveness of vaccines against potential agents of bioterrorism and emerging infectious diseases. Adjuvants activate the body's innate immune system—microbe-engulfing phagocytes and soluble immune stimulators—leading to effective adaptive immune responses by B cells, which make antibodies, and T cells, which can directly kill infected cells. Using high-throughput screening, several groups of researchers have identified, optimized, and developed adjuvants that are now in preclinical development.

- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NIAID)

Medical Countermeasures Against Nuclear and Radiological Threats: NIH is leading the HHS effort to sponsor and coordinate research to develop a means to counter the detrimental effects of a range of radiological threats. Most medical countermeasures to treat radiation injury are still in the early stages of development but are progressing. NIH-funded researchers recently (1) screened more than 40,000 candidate compounds and identified 52 candidates for evaluation as protective agents against the toxic effects of ionizing radiation, (2) developed improved forms of the chelating agent diethylenetriaminepentaacetic acid (DTPA), which animal testing data suggest can effectively clear the radionuclide americium-241 from the blood, and (3) studied 29 candidate drugs that are active against a broad range of radionuclides and might be useful in treating victims of radiological dispersion devices (“dirty bombs”).

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

Pandemic and Seasonal Influenza Vaccine Research: In FYs 2006 and 2007, NIH made significant progress toward the development of new and more effective vaccines for the control of both seasonal and pandemic influenza. For example, an NIH-supported clinical trial provided the scientific data on which the FDA based its recent licensure of the first pandemic influenza vaccine against H5N1 virus (“bird flu”) in the United States. NIH also developed and conducted clinical trials of whole-inactivated and live-attenuated vaccines against H5N1 influenza and developed DNA, recombinant virus, and recombinant protein-based influenza vaccines. NIH also supports activities to expand and accelerate the development of additional manufacturing methods; evaluate various strategies to optimize a limited vaccine supply, including intradermal vaccines and the use of adjuvants; and explore the concept of developing a vaccine that raises immunity to parts of the influenza virus that vary little from season to season and from strain to strain, thereby potentially reducing or eliminating the need for annual immunization against seasonal influenza. Such a vaccine might also strengthen protective immunity against an emerging pandemic strain of influenza virus.

- For more information, see http://www3.niaid.nih.gov/topics/Flu/understandingFlu/Prevention.htm

- For more information, see http://www3.niaid.nih.gov/topics/Flu/PDF/InfluenzaBlueRibbonPanel2006.pdf
- (E/I) (NIAID)

Radiation Event Medical Management (REMM): As a part of an effort to improve public health emergency preparedness and response, NIH and the HHS Office of the Assistant Secretary for Preparedness and Response announced in 2007 a new downloadable online diagnostic and treatment toolkit to guide health care providers during a mass casualty radiation event. The REMM toolkit includes easy-to-follow procedures for diagnosis and management of radiation contamination and exposure, guidance for the use of radiation medical countermeasures, and a variety of other features to facilitate medical responses to radiation emergencies.

- For more information, see http://remm.nlm.gov
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems.*
- (I) (NLM)

Infrastructure and Research Resources

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) 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, which use a multidisciplinary approach to research and development, (2) two National Biocontainment Laboratories (with BSL-4 capacity, the highest level of containment) and (3) 13 Regional Biocontainment Laboratories with BSL-3 capacity.

- For more information, see http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/PublicMedia/BioLabs.htm
- (E/I) (NIAID) (GPRA Goal)

The National Science Advisory Board for Biosecurity (NSABB): NSABB was established to advise the U.S. Government on strategies for the efficient and effective oversight of dual-use biological research, taking into consideration both national security concerns and the needs of the research community. The term “dual use” in conjunction with life sciences research is an acknowledgment that some of the information and technologies used to advance human, animal, and plant health can also be used to threaten public health and safety. NSABB brings together 25 voting non-Federal members who represent the scientific, biosafety, security, legal, ethics, scientific publishing, and intelligence communities. In addition, there is active participation by 14 major Federal departments, agencies, and offices across the Government. NSABB has issued two sets of reports and recommendations. The first is focused on the biosecurity issues raised by the rapidly increasing ability to synthesize select agents and other dangerous pathogens. The report identifies a number of biosecurity considerations; assesses whether the current Federal regulations, policies, and guidelines afford adequate oversight in this arena; and provides recommendations for addressing the issues. The second report is a proposed framework for local and Federal oversight of dual-use research. It is intended as a springboard for the development of Federal guidelines and procedures for oversight of dual-use research and includes guidance for identifying dual-use research of concern, considerations for developing codes of conduct for life scientists, and considerations and tools for the responsible communication of dual-use research. NSABB is currently developing strategies for fostering international engagement of dual-use life sciences issues and for education and outreach regarding these issues.

- For more information, see http://www.biosecurityboard.gov

- (O) (OD)

HIV/AIDS Research Network Restructuring: To better address the evolving scientific challenges of the HIV/AIDS epidemic, in FY 2006 NIH restructured its HIV/AIDS clinical research infrastructure into six research networks: the AIDS Clinical Trials Group (ACTG), the HIV Prevention Trials Network (HPTN), the HIV Vaccine Trials Network (HVTN), the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Group, the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), and the Microbicide Trials Network (MTN). Each network consists of a leadership group that provides administrative and technical support, as well as a number of the 73 HIV/AIDS Clinical Trials Units NIH funds in the United States and abroad (some Clinical Trials Units belong to more than one network). The reorganization will improve the efficiency, flexibility, and coordination of HIV/AIDS clinical research.

- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2007/ctu07.htm
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NIAID) (GPRA Goal)

Translational Research at Primate Research Centers: Nonhuman primates are critical components for translational research because of their close physiological similarities to humans. Nonhuman primates are widely 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 and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using nonhuman primates. In FY 2007, more than 1,000 research projects used nonhuman primates from these resources. Highlights of research activities include:

- Use of the simian immunodeficiency virus for AIDS-related research, including development of novel microbicides to prevent infection by the AIDS virus and testing of AIDS vaccines
- 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
- Sponsored scientific workshops in FYs 2006 and 2007 that further defined the genetic tools necessary for translational research using nonhuman primates

- For more information, see ncrr.nih.gov/comparative%5Fmedicine/resource_directory/primates.asp
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCRR)

Centers of Excellence for Influenza Research and Surveillance: Six Centers of Excellence for Influenza Research and Surveillance, established in 2007, significantly expand the ability of NIH to conduct research on different strains of animal and human influenza viruses collected internationally or in the United States. The centers will lay the groundwork for the development of new and improved control measures for emerging and reemerging influenza viruses, help determine the prevalence of avian influenza viruses in animals in close contact with humans, and extend understanding of how influenza viruses evolve, adapt, and are transmitted. The centers will also bolster research on questions such as how influenza viruses cause disease and how the human immune system responds to infection and will inform public health strategies to control and minimize the impact of seasonal and pandemic influenza.

- For more information, see http://www3.niaid.nih.gov/research/resources/ceirs

- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NIAID)

Urinary Tract Infections: NIH supports a Specialized Center of Research on Sex and Gender Factors Affecting Women's Health. This program advances new understanding of host-pathogen interactions that occur throughout the infectious cycle, including host defense response in the bladder and the virulence mechanisms by which bacterial pathogens subvert the defenses.

- For more information, see http://clinicaltrials.gov/ct/show/NCT00068120
- Justice SS, et al. *Proc Natl Acad Sci U S A* 2006;103:19884-9, PMID: 17172451
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK)

NIH Countermeasures Against Chemical Threats (CounterACT) Research Network: CounterACT, 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 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, is entering clinical trials in epilepsy patients through the NINDS 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.

- For more information, see http://www.ninds.nih.gov/funding/research/counterterrorism/index.htm
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (NINDS, NEI, NIAID, NIAMS, NIEHS, NIGMS)

Influenza Virus Resource: This database of more than 40,000 influenza virus sequences allows 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 by NCBI using data obtained from NCBI's Influenza Virus Sequence Database and from NIAID's Influenza Genome Sequencing Project, which has contributed sequences of the complete genomes from more than 2,500 influenza samples. In FY 2006 more than 11,000 influenza virus sequences were entered into the database, and new search and annotation tools were added to assist researchers in their analyses.

- Wolf YI, et al. *Biol Direct* 2006;1:34, PMID: 17067369
- Chang S, et al. *Nucleic Acids Res* 2007;35:D376-80, PMID: 17065465
- For more information, see http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html
- For more information, see http://www.niaid.nih.gov/dmid/genomes/mscs/influenza.htm
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*, Chapter 3: *Genomics*, and Chapter 3: *Molecular Biology And Basic Sciences*
- (I) (NLM)

Wireless Information System for Emergency Responders (WISER®): WISER is a system designed to assist first responders in hazardous material incidents by providing a wide range of information on hazardous substances, including substance identification support, physical characteristics, human health information, and containment and suppression advice. In 2007, several important features were added to WISER, including radiological support

with data for more than 20 isotope substances and tools/reference materials for radiological incidents. A new partnership with the U.S. Department of Transportation (DoT) enabled integration of the DoT's Emergency Response Guidebook (ERG) 2004 with WISER and the development of a stand-alone ERG 2004 Mobile version. Widely used by first responders, WISER is available for downloading onto electronic handheld devices and Windows-based platforms or for browsing on the Web.

- For more information, see http://wiser.nlm.nih.gov
- This example also appears in Chapter 3: *Technology Development*.
- (I) (NLM)

HIV/AIDS Epidemiological and Long-Term Cohort Studies: NIH supports epidemiological HIV research through a wide range of cohort studies that contribute to our understanding of risk factors that lead to HIV transmission and disease progression. Established in 2005, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) compiles data from NIH-funded international HIV research to answer population-level questions about HIV variants and resistance, HIV pathogenesis in different settings, success of antiretroviral therapy, treatment history of HIV in different populations, success of prevention strategies, and vaccines. The Pediatric HIV/AIDS Cohort Study (PHACS), established in 2005, addresses two critical pediatric HIV research questions: the long-term safety of fetal and infant exposure to prophylactic antiretroviral chemotherapy and the effects of perinatally acquired HIV infection in adolescents. The Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) are the two largest observational studies of HIV/AIDS in women and homosexual or bisexual men, respectively, in the United States. These studies exceed standard clinical care diagnostics and laboratory analysis on both HIV-infected, and, importantly, HIV-negative controls, which allows for novel research on how HIV spreads, how the disease progresses, and how it can best be treated. The studies focus on contemporary questions such as the interactions among HIV infection, aging, and long-term treatment; cardiovascular disease; and host genetics and their influence on susceptibility to infection, disease progression, and response to therapy.

- For more information, see http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (NIAID, NICHD)

National NeuroAIDS Tissue Consortium (NNTC): The NNTC is a repository of brain tissue and fluids from highly characterized HIV-positive individuals. Established as a resource for the research community, NNTC includes information from more than 2,000 individuals, including approximately 641 brains, thousands of plasma and cerebrospinal fluid samples, and additional organs and nerves of interest.

- For more information, see http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-08-021.html
- 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**, NINDS)

International Collaboration

Success in Treating Drug Addiction Internationally: International efforts to disseminate effective drug abuse treatments have seen success in countries with epidemic opiate addiction/HIV problems. Because of NIH research demonstrating that addiction is a chronic, relapsing disease that can be effectively treated, a culture change is starting to occur in these countries. For example, despite experiencing severe drug problems, Malaysia lagged behind in the treatment of drug addiction and related disorders, even as it coped with having the second-highest

HIV prevalence rate among adult populations and the highest proportion of HIV cases from injection drug use. Historically, drug abusers were "rehabilitated" involuntarily in correctional facilities. Although 60 percent of prisoners had drug-related offenses, no or minimal treatment was available in prison, and no medications were permitted. This primarily criminal treatment approach had limited effectiveness, which led to widespread public dissatisfaction and the recent introduction of medications for addiction. These include naltrexone (1999), buprenorphine (2001), and methadone (2003). These drug treatment programs, which were rapidly embraced by the country's medical community, have resulted in tens of thousands of opiate-dependent patients receiving medical treatment. Now, the Ministry of Health rather than the Ministry of Security has authority for providing medical treatment for heroin addiction. This shift signals a remarkable change in Malaysian policies and approaches to addiction and an important opportunity to develop, implement, and disseminate effective treatments. A similar success story is starting to unfold in China as well.

- Mazlan M, et al. *Drug Alcohol Rev* 2006;25:473-8, PMID: 16939945
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIDA, NIAID)

Multinational Influenza Seasonal Mortality Study: NIH is leading an international collaborative effort to analyze national and global epidemiological patterns associated with influenza virus circulation. Twenty countries have contributed data on mortality, virus surveillance, genomics, and control strategies. The goals of this large-scale collaboration are to evaluate and compare public health strategies to alleviate the impact of seasonal influenza in different countries and to understand the global circulation patterns of influenza and their impact on populations. A better understanding of influenza epidemiology worldwide can inform vaccine strain selection and strategies to mitigate future influenza pandemics.

- For more information, see http://origem.info/misms
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
- (O) (FIC)

HIV Vaccine Development: NIH supports research around the world to find a safe and effective vaccine against HIV. Since the first HIV vaccine trial in 1987, NIH has worked with its partners in academia, Government, the private sector, and non-Government organizations to conduct more than 100 HIV vaccine clinical trials that have enrolled more than 26,000 volunteers. In 2005, NIH formed the Center for HIV/AIDS Vaccine Immunology (CHAVI), a consortium of scientists committed to overcoming key scientific roadblocks to HIV vaccine development and to designing and testing HIV vaccine candidates. NIH is also involved in the Global HIV Vaccine Enterprise and the Partnership for AIDS Vaccine Evaluation (PAVE). Several clinical trials are testing vaccine candidates around the globe. Recently, however, two large vaccine trials stopped immunizations upon recommendation of a Data Safety Monitoring Board review. However, the new large-scale trial, called PAVE 100, is still under discussion and may begin in 2008. This trial will test whether an NIH-developed candidate vaccine can prevent acquisition of infection or progression of disease (using viral load as a surrogate marker) in those who become infected.

- For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/default.htm
- (E/I) (NIAID) (GPRA Goal)

Global Infectious Disease Research Training: A major barrier to improved treatment and control of infectious diseases is the scarcity in endemic countries of scientists with expertise in infectious disease research. This program supports institutions in the United States and developing countries to train scientists from developing

countries to engage in research on infectious disease other than HIV/AIDS. The program is contributing to the long-term goal of building sustainable research capacity in endemic infectious diseases in institutions in developing countries to enhance prevention, treatment, and control of infectious diseases that cause major morbidity and mortality in the developing world.

- For more information, see http://www.fic.nih.gov/programs/training_grants/gid.htm
- This example also appears in Chapter 3: *Research Training and Career Development.*
- (E) (FIC, NIAID)

HIV Research Training Programs: The AIDS International Training and Research Program (AITRP) builds institutional, national, and regional HIV research capacity in low- and middle-income countries. Over the past 19 years, this program has been responsible for many of the first generation of research scientists from these countries, with many more in the pipeline. The program offers multidisciplinary biomedical, behavioral, and social science research training to a wide range of professionals. Building on the AITRP, the Clinical, Operational and Health Services Research Training Program for HIV/AIDS and TB (ICOHRTA AIDS/TB) began in 2002 to strengthen the capacity for clinical, operational, and health services research in low- and middle-income countries where AIDS, TB, or both are significant problems. Through training health professionals that reach across the spectrum of clinical and public health research, this program is strengthening the capacity of scientists, program managers, and policymakers to evaluate and better implement large-scale prevention, treatment, and care interventions that are locally relevant and effective. Many local leaders of programs supported by the President's Emergency Plan for AIDS Relief have received or are receiving their research training through the AITRP and the ICOHRTA AIDS/TB programs.

- For more information, see http://www.fic.nih.gov/programs/training_grants/aitrp/index.htm
- For more information, see http://www.fic.nih.gov/programs/training_grants/icohrta/aids_tb.htm
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Research Training and Career Development.*
- (E) (FIC, NCI, NIAID, NHLBI, NIDA, NIDCR, NIMH, NINDS, NINR, OAR, ORWH)

Mechanisms of HIV Neuropathogenesis: Domestic and Global Issues: Neurological manifestations, including HIV dementia and opportunistic infections and tumors, are among the most threatening complications of HIV infection. Emerging data indicate that the prevalence of HIV-related neurological disease differs across regions of the world, suggesting that different subtypes of HIV may be more or less capable of causing neuropathology or that genetic variance among people in various regions of the world could affect susceptibility to HIV's neuropathological effects. NIH sponsored a meeting in the spring of 2007 to address these issues, resulting in the release of a funding announcement.

- For more information, see http://synapse.neurology.unc.edu/venice/
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-030.html
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (NIMH, NINDS, OAR)

HIV Virus Transmission From Primates to Humans: Through the International Research Scientist Development Award (IRSDA), FIC provides career development and research support to U.S. postdoctoral scientists in the formative stages of their careers to solidify their commitment to global health research. For example, under this program, FIC supported the career development of Dr. Nathan Wolfe, whose work in Cameroon advanced our understanding of how retroviruses enter into human populations and determined that the likely point of

transmission of the HIV occurred between primates and bushmeat hunters. Dr. Wolfe has now received the NIH Director's Pioneer Award. Co-funded by FIC and NIAID, this award builds on Dr. Wolfe's IRSDA-supported research and is enabling the establishment of the first global network to monitor the transmission of new viruses, including those causing pandemic disease threats such as Ebola, anthrax, and monkeypox, from animals into human populations. This hunter cohort distributed throughout key habitats will provide a framework for a range of research projects aimed at predicting and preventing disease emergence, including studies of risk factors associated with primary and secondary infections with zoonotic microorganisms, anthropological studies of hunting and meat processing practices that lead to exposure, and ecological studies of the animal and human populations that influence transmission among and between groups.

- Wolfe ND, et al. *Proc Natl Acad Sci U S A* 2005;102:7994-9, PMID: 15911757
- For more information, see http://www.fic.nih.gov/programs/training_grants/irsda.htm
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (FIC)

NIH Strategic Plans Pertaining to Infectious Diseases and Biodefense Research

National Institute of Allergy and Infectious Diseases (NIAID)

- *NIAID: Planning for the 21st Century (2000)*

HIV/AIDS

- *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis (2001)*
- *Vaccine Research Center Strategic Plan: Research Toward Development of an Effective AIDS Vaccine (2001)*

Infectious Diseases (non-biodefense, non-AIDS)

- *Blueprint for Tuberculosis Vaccine Development (1997)*

Biodefense and Emerging Infectious Diseases

- *NIAID Strategic Plan for Biodefense Research (2007 update)*
- *NIAID Strategic Plan for Biodefense Research (2002)*
- *NIAID Biodefense Research Agenda for CDC Category A Agents (2002)*
- *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens (2003)*
- *NIAID Expert Panel on Immunity and Biodefense (2002)*
- *NIAID Expert Panel Review of Medical Chemical Defense Research (2003)*
- *NIAID Expert Panel on Botulinum Toxins (2002)*
- *NIAID Expert Panel on Botulinum Diagnostics (2003)*
- *NIAID Expert Panel on Botulinum Neurotoxins Therapeutics (2004)*
- *Report of the Blue Ribbon Panel on Influenza Research (2006)*
- *NIAID Research Agenda Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis (2007)*

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)

- *Bringing the Power of Science to Bear on Drug Abuse and Addiction* (under revision)

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*

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* (Draft)

Office of AIDS Research (OAR)

- *FY 2008 Trans-NIH Plan for HIV-Related Research*
  CC, CSR, FIC, NCCAM, NCI, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM, **OAR**, OBSSR, OIR, ORD, ORWH

Other Trans-NIH Strategic Plans

- NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats
  NCI, NHLBI, **NIAID**, NIEHS

Summary of Research Activities by Disease Categories

Autoimmune Diseases

The immune system has always been considered the body's protector against disease-causing organisms and foreign bodies. The idea that a person's immune system could launch an attack against itself was so unthinkable that in 1900, bacteriologist and immunologist Paul Ehrlich coined the term horror autotoxicus *to describe the body's innate aversion to forming antibodies against itself. More than 40 years later, Mac Burnet postulated that a so-called "thymic censor" blocked the creation of autoantibodies—antibodies that attack the self rather than foreign bodies. Burnet suggested that these autoantibodies might be produced if the "thymic censor" malfunctioned. We now know that autoimmunity is the failure of the immune system to distinguish between self (the body's own cells, tissues, and organs) and non-self (disease-causing organisms and other foreign substances). When this happens, the immune system reacts as though the body is nonself and acts accordingly—it attacks. Burnet went on to win the Nobel Prize for subsequent work in immunology. He and Peter Medawar won the prize by demonstrating that the body can learn to not attack a foreign presence (e.g., a transplanted organ). This concept, called immune tolerance, is central to many of today's most important advances in immunology.*

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 disease 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 a heightened susceptibility. Some of the more common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, multiple sclerosis, systemic lupus erythematosus, 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, non-organ-specific diseases, such as systemic lupus erythematosus, 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, because most autoimmune diseases are more common in women than in men, hormones are suspected of playing a role. For these and other reasons, the autoimmune diseases are best recognized as a family of related disorders that must be studied together as well as individually.

Most autoimmune diseases disproportionately affect women and, as a group, are among the leading causes of death for young and middle-aged women[38]. Although treatments are available for many autoimmune diseases,

[38] Walsh SJ, Rau LM. *Am J Public Health* 2000;90:1463-6, PMID: 10983209

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, including NIAID, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIDDK, NCI, NIDCR, NINDS, the National Human Genome Research Institute (NHGRI), and NIEHS, collaborate with professional and patient advocacy organizations to support autoimmune disease research. The Autoimmune Diseases Coordinating Committee (ADCC) facilitates inter-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, and prevention interventions. However, NIH recognizes that more needs to be done to close the gaps in knowledge and achieve the overall goal of reducing the rising toll of autoimmune diseases. The major tasks facing researchers in autoimmune diseases are:

- Development of a mechanism-based, conceptual understanding of autoimmune diseases
- Translation of this knowledge into new, broadly applicable strategies for treatment and prevention of multiple diseases
- Development of sensitive tools for early and definitive diagnosis, disease staging, and identification of at-risk individuals

NIH supports an array of programs to accomplish these tasks, including research and activities to:

- Advance understanding of the distribution of autoimmune diseases through epidemiological studies
- Apply the knowledge provided by the Human Genome Project toward elucidating the hereditary risks of autoimmune diseases
- Extend understanding of genetic and environmental factors contributing to autoimmune diseases and then develop effective prevention strategies that arrest the autoimmune process before it can irreversibly damage the body
- Enhance the translation of scientific advances in autoimmune disease to clinical practice 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

In autoimmune diseases, a major goal of contemporary research is to “re-educate” the immune system by using tolerance induction strategies that aim to selectively block or prevent deleterious immune responses while leaving protective immunity intact. Immune tolerance will be evaluated by integrating mechanistic studies of tolerance induction and suppression of disease into clinical research studies and by conducting clinical trials of a variety of agents and strategies through dedicated clinical networks.

Overarching priority areas that promise to accelerate autoimmune disease research include biomarker development, bioinformatics, and application of new technologies. The development of biomarkers holds great promise for earlier and more accurate diagnosis of autoimmune diseases, better prediction of disease flare-ups, ceptibility genes and to study gene and protein patterns in tissue samples. They also 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-Institute 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 prevalence is rising. Examples of prevalence and incidence statistics for some autoimmune diseases are:

- An estimated 2.1 million people in the United States (about 1 percent of the population), including about 30,000 to 50,000 children, have rheumatoid arthritis[39].
- About 730,000 to 1.5 million people have type 1 diabetes (National Diabetes Fact Sheet, 2005). About 15,000 people younger than age 20 are diagnosed annually with type 1 diabetes[40].
- An estimated 250,000 to 350,000 people in the United States have been diagnosed with multiple sclerosis[41].
- In the United States, 239,000 people have been diagnosed with or are suspected to have systemic lupus erythematosus[42].
- As many as 1.4 million people in the United States have inflammatory bowel disease[43].

For more information, see http://www3.niaid.nih.gov/topics/autoimmune/PDF/ADCCFinal.pdf

NIH Funding for Autoimmune Disease Research

In FYs 2006 and 2007, NIH funding for autoimmune diseases research was $598 million and $587 million respectively. The table at the end of this chapter indicates some of the research areas supported by this investment (see “Estimates of Funding for Various Diseases, Conditions, and Research Areas”).

Summary of NIH Activities

NIH seeks to understand the onset and progression of autoimmune diseases and to use that knowledge to develop better interventions 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 means that research on one autoimmune disease often advances our understanding of others.

---

[39] Lawrence RC, et al. *Arthritis Rheum* 1998;41:778-99, PMID: 9588729

[40] For more information, see http://jama.ama-assn.org/cgi/content/abstract/297/24/2716

[41] Anderson DW, et al. *Ann Neurol* 1992;31:333-6, PMID: 1637140

[42] Lawrence RC, et al. *Arthritis Rheum* 1998;41:778-99, PMID: 9588729

[43] Loftus EV Jr. *Gastroenterology* 2004;126:1504-17, PMID: 15168363

Providing Research Resources and Infrastructure

Disease Registries

Many autoimmune diseases are rare, and researchers often must engage in national and international collaborativ research to ensure access to sufficient numbers of patients and tissue samples to conduct their studies. NIH provides resources to facilitate these research efforts. For example, disease registries provide an important epidemiological resource for tracing the natural history of autoimmune diseases, assessing its burden in different populations, and identifying and tracking trends in incidence and prevalence. NIH supports patient registries for numerous autoimmune diseases, including alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, epidermolysis bullosa acquisita, juvenile and adult-onset rheumatoid arthritis, lupus, neonatal lupus, and scleroderma. Some of these registries also contain relevant clinical data linked to tissue samples.

Other Research Resources

NIH-supported research resources also include programs for the preclinical development of therapeutic agents, such as the Type 1 Diabetes-Rapid Access to Intervention Development Program; biological specimen repositories; animal models; provision of genetic, genomic, and other molecular assays for specific projects; clinical trials infrastructure; and assistance in identifying collaborators. Some of these resources are mentioned in more detail in the "Notable Examples" later in this section.

Identifying Environmental Triggers of Autoimmune Diseases

Two large-scale projects that are searching for environmental triggers of autoimmune diseases are the Carolina Lupus Study and The Environmental Determinants of Diabetes in the Young (TEDDY) study. The Carolina Lupus Study, initiated in 1997, was the first population-based epidemiological study to examine the influence of hormonal and occupational exposures on lupus. The investigators found a striking association between occupational exposure to silica dust and lupus in individuals living in North and South Carolina. They also found that, compared with people who did not have lupus, patients with lupus were more likely to self-report occupational exposure to mercury, agricultural work that involved mixing pesticides, or work in a dental office or laboratory[44]. These and similar findings are expected to lead to improved prevention strategies for lupus and other autoimmune diseases and suggest possibilities for studies of the molecular development of lupus.

TEDDY is pinpointing environmental factors–such as infectious agents or diet–that can trigger type 1 diabetes in genetically susceptible individuals. This international consortium is following individuals who are at high genetic risk for type 1 diabetes from birth until age 15 to discover how environmental factors after birth contribute to the development of prediabetic autoimmunity and type 1 diabetes. Because type 1 diabetes and celiac disease share similar genetic predispositions, 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.

Understanding the Genetics of Autoimmune Diseases

NIH-supported scientists are identifying the genetic underpinnings of autoimmune disorders, research that can elucidate molecular pathways of disease and possible therapeutic targets. For example, investigators recently showed that a gene called PSORS1 plays a role in determining who gets psoriasis. Individuals with a particular form of this gene (the HLA-Cw6 allele) are more likely to develop early-onset psoriasis[45]. Scientists hope that further

---

[44] Cooper GS, et al. *J Rheumatol* 2004;31:1928-33, PMID: 15468355

[45] Nair RP, et al. *Am J Hum Genet* 78:827-51, PMID: 16642438

research will lead to a treatment that interferes with the disease by targeting the PSORS1 gene. Researchers also have discovered genes that variously appear to play roles in lupus, rheumatoid arthritis, inflammatory bowel disease, and alopecia areata, bringing us a step closer to understanding the mechanisms of these diseases[46].

Recent technological advances have led to the development of genome-wide association studies that compare the genomes of people with an illness to those of people without the illness. Through this comparison, it becomes possible to identify even subtle genetic differences between affected and unaffected people (see the *Genomics* section in Chapter 3 for more information about genome-wide association studies). Genome-wide analysis is beginning to yield important results in the study of autoimmune diseases. For example, recent studies have led to the identification of key genes involved in type 1 diabetes[47] and inflammatory bowel disease[48]. Recent technological advances have led to the development of genome-wide association studies that compare the genomes of people with an illness to those of people without the illness. Through this comparison, it becomes possible to identify even subtle genetic differences between affected and unaffected people (see the *Genomics* section for more information about genome-wide association studies). Genome-wide analysis is beginning to yield important results in the study of autoimmune diseases, including the identification of key genes involved in type 1 diabetes and IBD. In other research, investigators using a large familial dataset found the first new genes linked to MS in more than 20 years. These genes code for proteins that influence the way T cells patrol the body for pathogens, shedding light on a possible mechanism of MS onset and progression[49]. In a similar quest to identify disease genes, the Type 1 Diabetes Genetics Consortium is studying families with two or more siblings with type 1 diabetes. In addition, NIH supports the Genetic Association Information Network (GAIN), which provides genotyping services, including genome-wide association studies to enhance and extend the utility of existing of research efforts. Through GAIN, NIH supports a long-term collaboration in which investigators are seeking to identify new genetic susceptibility factors for the development of psoriasis."

Understanding the Mechanisms of Autoimmune Disease Onset and Progression

NIH sponsors research to illuminate the causes of autoimmune diseases and the regulatory mechanisms that control autoantibody production and function. For example, researchers recently used a mouse model to show that toll-like receptors, a set of immune receptors involved in the earliest immune responses to infection and long thought to play a key role in autoimmune responses, are indeed implicated. They showed that even minor mutations in toll-like receptors can spark autoimmunity, suggesting that this family of proteins could be an important therapeutic target for lupus or other autoimmune diseases[50]. Related research showed that a recently identified joint protein, cadherin 11, plays a role in rheumatoid arthritis in a mouse model of the disease. The investigators showed that a treatment that targets this protein prevents the abnormal adhesion and cartilage destruction typical of rheumatoid arthritis in mice, revealing a potential new therapeutic target in humans[51].

---

[46] Haan CK, Geraci SA. *Science* 2006;312:1665-9, PMID: 12022585, Haas CS, et al. *Arthritis Rheum* 2006;54:2047-60, PMID: 16804865 Martinez-Mir A, et al. *Am J Hum Genet* 2007;80:316-28, PMID: 17236136 Duerr RH, et al. *Science* 2006;314:1461-3, PMID: 17068223

[47] Lowe CE, et al. *Nat Genet* 2007;39:1074-82, PMID: 17676041

[48] Duerr RH, et al. *Science* 2006;314:1461-3, PMID: 17068223

[49] International Multiple Sclerosis Genetics Consortium. *N Engl J Med* 2007;357:851-62, PMID: 17660530

[50] Pisitkun P, et al. *Science* 2006;312:1669-72, PMID: 16709748

[51] Lee DM, et al. *Science* 2007;315:1006-10, PMID: 17255475

NIH supports a range of initiatives such as the following to better understand the mechanisms of autoimmune disease onset and progression and to develop effective interventions.

The Cooperative Study Group for Autoimmune Disease Prevention, established in 2001, is a collaborative network of investigators devoted to understanding the functioning of the immune system in both health and autoimmune disease. The Study Group works to develop the knowledge base necessary to design safe and effective interventions for the prevention of autoimmune disorders. Participating centers support preclinical research, innovative pilot projects, and noninterventional clinical studies, with an emphasis on type 1 diabetes. The Study Group, renewed recently for another 5 years, includes six cooperative agreements among researchers across the Nation.

The Beta Cell Biology Consortium (BCBC) is a team science initiative established in 2001 and competitively continued in 2005. This program facilitates interdisciplinary approaches to advance the understanding of insulin-producing pancreatic beta cell development and function. Currently, BCBC consists of 29 scientists, the majority of whom participate as investigators on 10 cooperative agreements. Scientists from two intramural NIH laboratories also are involved. In addition to conducting research, the Consortium develops research resources, such as antibodies, mouse models, and gene arrays, for use by the scientific community.

Scientists studying autoimmune diseases are excited about the emerging research approach known as systems biology that seeks to understand the overall behavior of biological systems. Systems biology uses computational methods to analyze data or simulate the system of interest and requires collaboration among researchers from bioinformatics, computer science, molecular biology, genomics, and other disciplines. NIH-supported researchers are applying a systems biology approach to better understand SjÓgren's syndrome, an autoimmune disorder in which immune cells attack and destroy the glands that produce tears and saliva, and other salivary gland disorders. Salivary gland biology is conducive to systems biology because researchers already have extensively catalogued the genes and proteins expressed in salivary glands. The scientific opportunity is to create an integrative, quantitative, and dynamic model encompassing every known aspect of the molecular and cellular biology of salivary glands and to translate this model into precise and practical ways to treat SjÔgren's syndrome.

Improving the Diagnosis and Prognosis of Autoimmune Diseases

Biomarker research is one area of investigation that may lead to better techniques for diagnosing autoimmune disorders. Biomarkers, clinical signs that correlate with the onset or progression of disease, already are commonly used to help diagnose some diseases, including prostate cancer and certain types of heart disease. With the rise of technologies to identify and test biomarkers more quickly, this area of research holds great promise for earlier and more accurate autoimmune disease diagnosis, better prediction of disease flare-ups, 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. For example, researchers have identified biomarkers that can be detected in the urine of patients with kidney disease and that provide information about the type and severity of disease[52]. If validated with further research, these biomarkers may provide the basis for a noninvasive test to replace repeated kidney biopsies in patients with lupus, who are at increased risk for potentially severe kidney disease.

The Biomarkers Consortium, of which NIH is a founding partner, recently approved the concept for a systemic lupus erythematosus Biomarkers Working Group. The Consortium is a public-private partnership that endeavors to

[52] Varghese SA, et al. *J Am Soc Nephrol* 2007;18:913-22, PMID: 17301191

discover, develop, and qualify biomarkers to identify risk for disease, make a diagnosis, and guide treatment. The systemic lupus erythematosus Biomarkers Working Group will focus on identifying and validating biomarkers for prognosis and assessment of lupus disease activity, with the goal of speeding drug discovery and evaluation of new therapies in a disease that has not had a new drug approved in 40 years. This work also may lead to the identification of common biomarkers for other autoimmune diseases.

Developing Evidence-Based Treatment and Prevention Interventions

NIH supports the development of effective clinical strategies to prevent and treat autoimmune diseases and the translation of successful strategies to clinical application. The following programs and initiatives highlight NIH's work in this area.

The Autoimmunity Centers of Excellence (ACEs) encourage and enable collaborative research–across scientific disciplines and medical specialties, and between basic and clinical scientists–to test prevention and treatment interventions. 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. ACE currently is supporting 10 active clinical trials studying treatments for lupus, multiple sclerosis, pemphigus vulgaris, rheumatoid arthritis, and SjÔgren's syndrome.

The Clinical Islet Transplantation Consortium develops and implements a program of single- and multicenter clinical studies, with accompanying mechanistic studies, in islet transplantation for the treatment of type 1 diabetes. The Consortium is focused on improving the safety and long-term success of methods for transplanting islets, the insulin-producing cells of the pancreas, in people whose own islets have been destroyed by the autoimmune process that characterizes type 1 diabetes. Some studies will focus on improving combined islet and kidney transplants in patients with type 1 diabetes who have kidney failure, a common diabetes complication.

The Immune Tolerance Network (ITN) is a collaborative research effort to study and test new drugs and therapies for autoimmune diseases and other immune-related disorders. ITN studies are based on stimulating immunological tolerance, the mechanism by which the immune system naturally avoids damage to self.

Today, autoimmune diseases are commonly managed with immunosuppressive agents. Because these agents broadly reduce the immune response, they place patients at increased risk for infection. The ITN supports four clinical studies with the goal of identifying and developing interventions that selectively target harmful autoimmune responses, avoiding the burdensome and dangerous side effects of global immunosuppression. For example, researchers are evaluating agents that suppress the activity of proteins known to be involved in the pathology of many autoimmune diseases. These proteins include the major histocompatibility complex, large protein clusters that are heavily involved in immune function; T cell receptors, which help lymphocytes (a type of immune cell) recognize foreign material; and autoantigens, normal proteins or other molecules that are mistakenly recognized by the immune system.

The development of therapeutic vaccines is a promising approach being taken by ITN scientists. One therapeutic vaccine in development, called the "universal" major histocompatibility complex (MHC) class II peptide vaccine, might be used to treat a wide variety of autoimmune disorders. The vaccine's target peptide–a short portion of a protein–is present in many of the molecules known to be associated with the pathology of rheumatoid arthritis. Because of this "universality," one vaccine can be used to simultaneously disrupt multiple molecular pathways of rheumatoid arthritis, increasing the likelihood of treatment success.

One clinical trial of special note is the Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial. The SCOT trial will compare the potential benefits of stem cell transplant and high-dose monthly cyclophosphamide (Cytoxan) in the treatment of scleroderma. This approach differs from current organ-specific treatments by seeking to treat the immune system as a whole.

Addressing the Comorbidities of Autoimmune Diseases

Another strategy for reducing the burden of disease is to support research to understand, prevent, diagnose, and treat comorbidities that affect many patients with autoimmune diseases. Comorbidities range from the presence of more than one autoimmune disease to conditions arising from immune attack on various body tissues or the interventions necessary to treat autoimmune disease. For example, a study of families with vitiligo, a pigmentation disorder in which white patches of skin appear on different parts of the body, found that family members of patients with vitiligo are predisposed to other, potentially more serious, autoimmune diseases[53]. This finding may increase the ability to diagnose autoimmune diseases earlier, which could lead to better treatment.

Patients with type 1 diabetes are at increased risk for 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[54]. In other research, investigators have identified potential molecular targets for prevention or treatment of chronic periodontitis, which can be a complication of diabetes[55].

Notable Examples of NIH Activity

Key for Bulleted Items:

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported through a congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = Concerns progress tracked under the **G**overnment **P**erformance and **R**esults **A**ct

Providing Research Resource and Infrastructure

Type 1 Diabetes–Rapid Access to Intervention Development (T1D-RAID): Many investigators who have discovered promising therapeutic agents in the laboratory do not have the resources to ready the agents for use in human

---

[53] Laberge G, et al. *Pigment Cell Res* 2005;18:300-5, PMID: 16029422

[54] Nathan DM, et al. *N Engl J Med* 2005;353:2643-53, PMID: 16371630;
For more information, see http://diabetes.niddk.nih.gov/dm/pubs/control/#study

[55] Muthukuru M, Cutler CW. *Infect Immun* 2006;74:1431-5, PMID: 16428799

clinical trials. Therefore, NIH supports the T1D-RAID program to provide resources for preclinical development of agents to test in clinical trials. For example, the drug lisofylline, which was prepared and tested under the T1D-RAID program, will be studied in an upcoming pancreatic islet transplantation clinical trial.

- For more information, see http://www.t1diabetes.nih.gov/T1D-RAID/index.shtml
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (**NIDDK**, NCI)

Identifying Environmental Triggers of Autoimmune Diseases

Carolina Lupus Study: Since 1997, NIH has supported the Carolina Lupus Study, the first population-based epidemiological study to examine the influence of hormonal and occupational exposures, as well as the genetic factors that affect immune function and metabolism, on systemic lupus erythematosus. Lupus is a severe, disabling autoimmune disease that can lead to morbidity and mortality from renal and cardiovascular disease. African Americans are two to three times more likely than Whites to develop the disease, for unknown reasons. The study included 265 patients and 355 people without lupus living in 60 counties in North and South Carolina. The results of analysis of occupational exposure to silica dust in relation to risk for systemic lupus erythematosus were striking. Other associations were seen with self-reported occupational exposure to mercury, in mixing pesticides for agricultural work, and among dental workers. Weaker associations were seen between systemic lupus erythematosus and shift work and among health care workers with patient contact.

- For more information, see http://www.niehs.nih.gov/research/atniehs/labs/epi/studies
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NIEHS)

Understanding the Genetics of Autoimmune Diseases

Multiple Sclerosis: While the exact cause of multiple sclerosis is unknown, research suggests a strong genetic component. NIH funds a number of studies to determine the underlying genetic causes of multiple sclerosis, including a project to identify regions of the genome containing multiple sclerosis susceptibility genes by using a large familial dataset and genomic analysis tools. NIH also funds clinical trials to test therapies for multiple sclerosis, including the CombiRx trial, a randomized, controlled clinical trial comparing the efficacy of treatment combining interferon-beta and glatiramer acetate versus treatment with a single agent for relapsing forms of multiple sclerosis. A study conducted in conjunction with CombiRx by NIH intramural researchers (BioMS) is assessing multiple sclerosis biomarkers by using genomic and proteomic technology and relating the information obtained back to clinical and MRI data generated by the CombiRx clinical trial.

- Gregory SG, et al. *Nat Genet* 2007;39:1083-91, PMID: 17660817
- International Multiple Sclerosis Genetics Consortium, et al. *N Engl J Med* 2007;357:851-62, PMID: 17660530
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NINDS)

Autoimmune Diseases and Genetics: With the advancement of genomic science, more information has been gained about the genetic component of autoimmune diseases. Susceptibility genes have been identified for rheumatoid arthritis, lupus, psoriasis, and alopecia areata. Understanding the genetic influence of these diseases provides essential information for the design of new therapies.

- Kumar KR, et al. *Science* 2006;312:1665-9, PMID: 16778059
- Nair RP, et al. *Am J Hum Genet* 78:827-51, PMID: 16642438

- Haas CS, et al. *Arthritis Rheum* 2006;54:2047-60, PMID: 16804865
- Martinez-Mir A, et al. *Am J Hum Genet* 2007;80:316-28, PMID: 17236136
- Remmers EF, et al. *N Engl J Med* 2007 Sep 6;357:977-86, PMID: 17804842
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/lupus_susceptibility_gene.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/psoriasis_gene.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/three_genes_ra.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/alopecia_areata.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/09_06.asp
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (**NIAMS**, NCRR, NHLBI, NIAID, NIMH)

Genetic Susceptibility for Alopecia Areata: Scientists supported by NIH have identified loci on four chromosomes that appear to play a role in the development of alopecia areata, an autoimmune disease characterized by hair loss that can affect the whole scalp or, in rarer cases, the entire body. Many U.S. families recruited for the study were identified through the Alopecia Areata Registry.

- Martinez-Mir A, et al. *Am J Hum Genet* 2007;80:316-28, PMID: 17236136
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/alopecia_areata.asp
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (**NIAMS**, NIMH)

Understanding the Mechanisms of Autoimmune Disease Onset and Progression

The Cooperative Study Group for Autoimmune Disease Prevention: In 2006, NIH renewed the Cooperative Study Group for Autoimmune Disease Prevention, which was established in 2001. This collaborative network is devoted to understanding immune homeostasis in both health and autoimmune diseases and to developing interventions to prevent autoimmune disease. The six participating Centers support preclinical research, innovative pilot projects, and noninterventional clinical studies, with an emphasis on type 1 diabetes. By the end of 2006, grantees had published 109 original research papers, and 5 of 48 pilot projects had matured into investigator-initiated grants. Of note, the Centers are collaborating on the “Roadmap to Inflammation in the NOD [non-obese diabetic] Mouse” project, which will identify and characterize genes and proteins involved in the development of diabetes and study the mechanisms by which diabetes develops.

- For more information, see http://fathmanlab.stanford.edu/roadmap_study_design.html
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (**NIAID**, NIDDK)

Systems Biology Approach to Salivary Gland Physiology: Previous research has catalogued the genes and proteins expressed in the salivary glands. This initiative puts those catalogues into context by defining when and where genes and proteins are expressed and how they function as parts of a fully integrated biological system. The initiative combines the power of mathematics, biology, genomics, computer science, and other disciplines to translate this highly detailed information into more precise and practical leads to treat SjÔgren’s syndrome, a debilitating autoimmune disorder that affects millions of Americans. The initiative also will help in learning to use saliva as a diagnostic fluid for a variety of conditions, from AIDS to cancer to diabetes.

- For more information, see http://www.nidcr.nih.gov/GrantsAndFunding/See_Funding_Opportunities_Sorted_By/ConceptClearance/CurrentCC/SysAppySal.htm
- For more information, see http://grants2.nih.gov/grants/guide/rfa-files/RFA-DE-08-001.html
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E) (NIDCR)

Beta Cell Biology Consortium (BCBC): The BCBC is collaboratively pursuing key challenges relevant to the development of therapies for type 1 and type 2 diabetes, including studying pancreatic development to understand how insulin-producing beta cells are made, exploring the potential of stem cells as a source for making islets, and determining the mechanisms underlying beta cell regeneration. The BCBC has generated key research resources, such as animal models, microarrays, and antibodies, which are available to the scientific community.

- For more information, see http://www.betacell.org
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*
- (E) (NIDDK)

Promising New Route to Rheumatoid Arthritis Therapy: Rheumatoid arthritis is a debilitating autoimmune disease that is characterized by joint inflammation and affects approximately 2.1 million Americans. In this disease, a thin membrane of the joint, the synovium, overgrows and attaches abnormally to cartilage, leading to its erosion. A recently identified joint protein, cadherin 11, mediates the disease in a mouse model. Blocking synovium attachment to cadherin 11 prevents this abnormal adhesion and cartilage destruction in mice and reveals a potential new therapeutic target for the disease in humans.

- Lee et al. *Science* 2007;315:1006-10, PMID: 17255475
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cad_11.asp
- (E) (NIAMS)

New Molecular Targets to Halt Periodontal Bone Loss: Approximately 80 percent of American adults have some form of periodontal disease. Chronic periodontitis erodes supporting structures of the tooth, leading to tooth loss. The risk of periodontal diseases is higher in smokers and individuals with diabetes; 18 million Americans suffer from diabetes and related complications, including increased incidence and severity of periodontitis. This higher incidence and severity are associated with increased cell death in bone- and tissue-forming cells called osteoblasts and fibroblasts. The loss of these cells results in decreased capacity to repair tissue and bone. NIH-supported investigators published two separate papers describing the mechanisms by which the diabetic state enhances cell death. The papers suggest that diabetes-induced cell death and compromised tissue repair are mediated by the TNF-a pro-apoptotic pathway, and the major effector is caspase-3. Inhibition of TNF-a or caspase-3 activity reduces cell death and restores repair capacity. Discrimination between harmful microbes and commensal species is a critical property of the mucosal immune system, which is essential for maintaining health. Host immune cells have surface receptors that recognize bacterial species such as those known to be associated with periodontitis. Host immune cells can selectively learn to respond strongly or to tolerate endotoxin produced by recognized bacteria. NIH-supported scientists found that patients with chronic periodontitis overproduce a molecule known as SHIP, which plays an important regulatory role in signaling immune cells to tolerate endotoxin. The data from these studies suggest possible targets for developing new ways to treat or prevent chronic periodontitis.

- Al-Mashat HA, et al. *Diabetes* 2006;55:487-95, PMID: 16443785
- Liu R, et al. *Am J Pathol* 2006;168:757-64, PMID: 16507891

- Muthukuru M, Cutler CW. *Infect Immun* 2006;74:1431-5, PMID: 16428799
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCR)

Trans-NIH Initiative for Translational Research in Immunology, Autoimmunity, and Inflammation: A new, trans-NIH initiative is being developed by the intramural research program to facilitate the translation of advances in basic immunology to improved therapies and clinical care for immune-mediated diseases. The translation of basic immunology to the clinic has been impeded by separations between basic immunologists, physicians, and epidemiologists and by barriers among clinicians who address diseases that share pathophysiologic mechanisms but are historically separated in different specialty practices. The new program will integrate research efforts not only across the basic, clinical, and population sciences but also across conventional medical subspecialties. Research will focus on a variety of autoimmune diseases, congenital and acquired immunodeficiency syndromes, processes in which inflammation or altered immunity has a pathogenic role, and malignant diseases influenced by the immune system. Studies will address the underlying role of the immune system and the similarities and differences of the inflammatory response in many seemingly unrelated immune-mediated diseases. The initiative is expected to advance understanding of the causes of the diseases and to promote the development of new therapies. It also is expected to serve as a model for future trans-NIH translational research efforts to facilitate more rapid development and testing of new therapies and enhance interdisciplinary training.

- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (I) (**NHLBI**, NIAID, NIAMS, NIDDK)

Improving the Diagnosis and Prognosis of Autoimmune Diseases

Monitoring Organ Rejection Using MRI: Organ transplants give patients a new lease on life. However, preventing the immune systems from rejecting the transplanted organ sometimes presents a challenge. Physicians must strike a balance between suppressing the immune system so that it does not reject the organ and maintaining enough immune activity to ward off infections. Tracking how the body accepts the new organ is critical to this process. The current “gold standard” for monitoring organ rejection is tissue biopsy, an invasive procedure in which a physician removes a small sample of the transplanted organ for testing. Biopsy has two drawbacks: patient discomfort (the physician must perform the procedure multiple times) and poor selectivity (biopsy removes tissue from only a limited number of sites and can miss rejection starting elsewhere in the organ). To overcome these limitations, NIH-supported researchers are developing a new method to monitor organ rejection with MRI. They label macrophages (immune cells) with polymer-coated, micron-sized iron oxide particles. These magnetic particles allow the migration of the macrophages to rejection sites in the transplanted organ to be clearly tracked by MRI. At present, this work is being performed on rats, but the investigators are extending it to large animals and humans. If successful, the approach could be used to optimize the administration of immunosuppressant drugs in clinical situations.

- Wu YL, et al. *Proc Natl Acad Sci U S A.* 2006;103:1852-7, PMID: 16443687
- For more information, see http://www.nibib.nih.gov/HealthEdu/eAdvances/25Sep06
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIBIB)

Developing Evidence-Based Treatment and Prevention Intervention

The Immune Tolerance Network: In 2007, NIH renewed support for the Immune Tolerance Network (ITN), a consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. The ITN studies and

tests new drugs and therapies for autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells. ITN studies are based on stimulating immunological tolerance, the mechanism by which the immune system naturally avoids damage to self. Immune tolerance approaches aim to "re-educate" the immune system to eliminate harmful immune responses and graft rejection while preserving protective immunity against infectious agents. The ITN has established state-of-the art core laboratory facilities to study the underlying mechanisms of candidate therapies and to monitor tolerance. In 2006, the ITN reported that a novel DNA-based ragweed allergy therapy could achieve long-lasting symptom reduction after only 6 weeks of therapy, compared with current methods that require years of biweekly injections. Current ITN studies include pancreatic islet transplantation for type 1 diabetes, approaches to slow or reverse the progression of autoimmune diseases, approaches to treat and prevent asthma and allergic disorders such as food allergy, and therapies to prevent liver and kidney transplant rejection without causing harmful suppression of immunity.

- For more information, see http://www.immunetolerance.org/
- For more information, see http://content.nejm.org/cgi/content/abstract/355/14/1445
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAID)

Addressing the Comorbidities of Autoimmune Diseases

Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC): The 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 EDIC study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients should begin intensive therapy as early as possible. EDIC recently found that recurrent hypoglycemia associated with intensive control does not affect patients' long-term cognitive function. After more than 20 years of studying this patient cohort, crucial insights continue to emerge.

- For more information, see http://www.bsc.gwu.edu/bsc/studies/edic.html
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDDK)

Comorbidities: Many autoimmune diseases affect multiple organ systems. Recent studies have identified the basis of concurrent diseases at a molecular level, as well as clinically. A biomarker for lupus-related kidney disease has led to a noninvasive diagnostic breakthrough. Patients with the skin pigmentation disease vitiligo are at increased risk for other autoimmune diseases. In addition, recent studies document an increased risk for cardiovascular disease among patients with rheumatoid arthritis.

- Laberge G, et al. *Pigment Cell Res* 2005;18:300-5, PMID: 16029422
- Giles GT, et al. *Arthritis Res Ther* 2005;7:195-207, PMID: 16207349
- Varghese SA, et al. *J Am Soc Nephrol* 2007;18:913-22, PMID: 17301191
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/lupus_kidney.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/vitiligo_risk.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/journal_special_text.asp
- (E) (**NIAMS**, NCRR, NHLBI, NIAID)

Vitiligo: Vitiligo is a skin disease characterized by a loss of pigment in all people who are affected. The psychological and social consequences can be particularly profound in affected people of color. A study of 133 families with vitiligo found that family members–even those who do not have vitiligo–are also predisposed to other, potentially more serious autoimmune diseases.

- Jin Y, et al. *N Engl J Med* 2007;356:1263-6, PMID: 17377159
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/04_10.asp
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (**NIAMS**, NIAID, NIDDK)

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*
- *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 (2000)*
- *NIAID Plan for Research on Immune Tolerance (1998)*
- *Report of the Expert Panel on Food Allergy Research (2006)*
- *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

Summary of Research Activities by Disease Categories
Chronic Diseases and Organ Systems

Two-year-old Hannah's[56] great-grandmother, who was born in 1900, died of tuberculosis in her thirties. Polio crippled her grandfather, and other family members died at young ages of influenza and typhoid fever. Dramatic improvements in public health and medical practice have made it considerably less likely that these and many other infectious diseases will pose the same threat to Hannah that they did to her ancestors. However, she and her family will almost certainly be affected by one or more chronic diseases and conditions—for example, type 2 diabetes, and obesity—whose incidence has risen dramatically in the United States as the burden of infectious disease has diminished. Even more worrisome is that although we think of many chronic diseases as more often affecting adults, such conditions are increasingly appearing in the young. For example, some 16 percent of American children between the ages of six and 19 are overweight [57]—a number unprecedented in history—placing them at greatly increased risk of type 2 diabetes, depression, and, as they grow to adulthood, heart disease and a host of other life-threatening conditions. In fact, former Surgeon General Richard Carmona has said that today's obese children could be the first generation of Americans with a life expectancy less than that of their parents, to say nothing of the effects of obesity-related conditions on their quality of life. As the burden of chronic disease in children and adults continues to grow in the United States and around the world, biomedical research to understand, predict, prevent, and treat chronic disease is critical.

Introduction

A chronic disease is one that lasts 3 months or longer. In general, chronic diseases cannot currently be prevented by vaccine or cured by medication, nor do they resolve on their own. 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. Health-damaging behaviors, such as tobacco use, lack of physical activity, poor eating habits, and excessive alcohol use contribute to many chronic diseases, whereas others may represent the long-term effect of early exposure to toxins and/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.

Many of the most burdensome chronic diseases develop over time and become more prevalent with age; less commonly, chronic disease may manifest from birth as a result of one or more faulty genes. Chronic diseases can be common in the U.S. population (e.g., heart disease, the leading cause of death), relatively rare (e.g., cystic fibrosis, which affects approximately 30,000 Americans), or represent a growing medical problem (e.g., type 2 diabetes and obesity).

Most chronic diseases and conditions affect one or more organs. 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 the quality of life for those living with these often debilitating conditions.

This section focuses primarily on a number of major chronic diseases within NIH's purview. 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), “Autoimmune Diseases” (e.g., lupus, multiple sclerosis), and “Infectious Diseases and Biodefense” (e.g., HIV/AIDS). Because some people with certain chronic diseases require transplantation to replace a diseased organ or tissue, organ transplantation research is highlighted in this section. Research on complementary and alternative medicine (CAM) approaches to combating chronic disease also is discussed. Finally, 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 can also be found at the NIH Pain Consortium Web site.

Burden of Illness and Related Health Statistics

The prevalence and burden of chronic diseases are substantial. In fact, the burden of chronic diseases is rapidly increasing worldwide. In 2005, chronic diseases contributed approximately 60 percent of the 58 million total reported deaths in the world and almost three-quarters of the burden of disease (measured in disability-adjusted life-years) in those age 30 or older. By 2015, deaths from chronic disease will be the most common cause of death even in the poorest countries.[58] Considering the totality of chronic diseases in the United States, more than 7 percent of adults age 45 to 54 have three or more chronic conditions and 36 percent of adults age 75 and older have three or more chronic conditions. Chronic disease disables or limits activity for almost 12 percent of all adults and more than 34 percent of adults age 65 and older. Moreover, annual mortality from chronic diseases in the United States is more than 1.7 million. For details on the depth and breadth of this burden, see the table of data, presented by disease and condition, at the end of this section.

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.[59] Coronary heart disease, the most common type of heart disease, occurs when the arteries that supply blood to the heart muscle become hardened and narrow. Coronary heart disease can cause angina (chest pain) or a heart attack and, over time, contribute to serious disability or death. Other chronic, serious cardiovascular conditions include hypertension, heart failure, atrial fibrillation, and peripheral arterial disease. Rare cardiovascular disorders include Marfan syndrome, a connective tissue disorder that affects growth and development, including the heart and blood vessels; 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,[60] causes airflow obstruction in the lungs that makes breathing difficult.Asthma, the most common chronic disease of childhood, is characterized by inflamed or swollen airways. Asthma can be controlled so that individuals have fewer and less frequent symptoms or can be more active. 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.[61]

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 properly use insulin (type 2). Diabetes can result in complications such as heart disease, stroke, hypertension, and nerve damage. It is also 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.

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 it is used 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. BMI numbers are interpreted differently for children; however, as with adults, rates of overweight and obesity have risen dramatically for children 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, sleep apnea, and 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; between 1990 and 2000, the number of people with kidney failure requiring dialysis or transplantation doubled.

Digestive and Urologic Diseases: Diseases of the digestive system involve many organs (e.g., intestine, 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 can sometimes 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 disease 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. Conversely, clotting disorders such as deep vein thrombosis can lead to the formation of life-threatening blood clots.

Musculoskeletal Disease: 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.

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. Chronic wounds on the skin or impaired wound healing are common in elderly, bed-ridden, and diabetic populations.

Eye Diseases and **Deafness:** Diseases of the eyes and ears can lead to chronic impairment or loss of vision and hearing. Middle ear infections (otitis media) can cause temporary hearing loss in children that can become permanent. Age-related macular degeneration (loss of cells in the retina) or hearing loss can reduce independence and quality of life in the elderly. Uveitis (inflammation of the eye) and glaucoma (damage to the optic nerve) are significant causes of

new blindness in adults.

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 and **Addiction:** Mental disorders are the leading cause of disability in the United States and Canada. Mental illness can also coexist with a number of other chronic diseases. For example, unipolar depressive disorder, a major contributor to disability worldwide, can be triggered by chronic diseases such as cancer or stroke in those who are prone to the disorder. Conversely, depression is associated with an increased risk for other diseases, such as coronary heart disease. Mental disorders often co-occur with alcohol dependence and other substance abuse, making treatment of either disorder more difficult. Addictions to alcohol and other drugs of abuse also are chronic diseases that have both physiological and behavioral components.[62]

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. 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 Diseases, Conditions, and Research Areas"). 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.

Summary of NIH Activities

To alleviate the public health burden of chronic diseases, NIH supports research on the development and progression, detection and diagnosis, prevention, and treatment and management of these diseases. Because of the impact such diseases have on public health and the national economy, NIH directs significant resources toward the study of common chronic diseases, such as asthma, heart disease, diabetes, and many others. However, NIH also support research on many less common chronic conditions. This research has the potential to improve the health and quality of life of thousands of Americans who suffer with these "rare" diseases but also can yield fundamental information on normal physiology as well as the pathophysiology of other, more common diseases. For example, long QT syndrome, which results from genetic mutations that lead to disruption of the normal electrical rhythms of the heart, affects an estimated 1 in 5,000 individuals and results in 3,000 deaths per year in the United States. However, studies of long QT syndrome also have shed light on the causes and treatments of more common, nongenetic cardiac arrhythmias that contribute to 300,000 sudden deaths each year.

This section highlights some key examples of challenges, progress, and emerging opportunities in NIH-

supported research on chronic diseases and organ systems. Through its multifaceted research efforts, NIH is providing a solid foundation for improved patient health and well-being.

Understanding Fundamental Mechanisms of Organ Health and Disease

Basic research supported by NIH provides the foundation for understanding and addressing chronic diseases. Understanding fundamental biological mechanisms at the molecular, cellular, tissue, and organ levels provides the basis for formulating new theories of disease causation, identification of novel treatment targets, and development of innovative strategies for disease prevention, diagnosis, or treatment. For example, NIH has made advances in understanding the mechanisms of chronic periodontitis, a disease that leads to tooth loss and affects 80 percent of the U.S. adult population. NIH-supported scientists have discovered that patients with chronic periodontitis have elevated levels of SHIP, a protein that impairs their ability to mount a robust immune attack on bacteria associated with the disease. In another study, NIH-supported scientists identified two pathways associated with chronic periodontitis in diabetic patients who experience increased incidence and severity of this disease. Although studied in different contexts, each of these advances paves the way for potential new targets for preventing or treating this highly prevalent disease. In another effort to increase understanding of the mechanisms of a chronic disease, NIH has initiated a Specialized Center of Clinical Research focused on understanding the key structural and regulatory processes mediating mucus clearance and their dysfunction in cystic fibrosis and COPD. The concepts emerging from the center are expected to stimulate development of new therapies to enable treatment early in the course of disease.

Some diseases, such as drug and alcohol addiction, affect nearly every organ system. NIH supports research to uncover fundamental mechanisms of alcohol-induced tissue injury that are common to many organs and tissues throughout the body, including the brain and liver. Program initiatives to elucidate the underlying mechanisms of alcohol-induced tissue injury will lead to the identification of biomarkers for early detection of disease and new strategies for treatment. Other diseases, such as osteoporosis, have a more limited but still significant impact on the body by affecting key tissues or organs. Because bone loss occurs without symptoms, people may not know that they have osteoporosis until a sudden strain, bump, or fall causes a disabling fracture. NIH supports a number of research projects aimed at elucidating the underlying mechanisms of osteoporosis and other bone diseases. Still other chronic diseases, such as diabetes, affect multiple organs and body systems but might be effectively treated or even cured by replacing a single type of tissue. For example, death of the insulin-producing beta cells of the pancreas results in type 1 diabetes, whereas type 2 diabetes arises when beta cells are present but not working properly. The NIH-supported Beta Cell Biology Consortium is studying how beta cells are made during development, maintained in sufficient numbers in healthy individuals, and function to release insulin in precise response to the body's needs. This research will provide the foundation for strategies to replace beta cells in patients with type 1 diabetes and to repair defective beta cells in those with type 2 diabetes.

A related line of inquiry is the study of processes that may either contribute to or signify the presence of chronic disease. For example, inflammation is a normal and necessary reaction of the body to infections, chemical irritants, and other harmful substances or injury. However, unresolved or chronic inflammation underlies or contributes to many chronic diseases. Researchers are working to elucidate the role of inflammation in a number of chronic diseases; for example, using a mouse model of glaucoma, researchers have discovered that a key inflammation marker, TNF-a, might be the link between elevated eye pressure and damage to the optic nerve. Another team found that resolvin E1, a form of omega-3 fatty acid, can alter the course of inflammation associated with periodontitis. In addition, researchers

are building on advances in the fundamental biology of inflammation to investigate age-related inflammatory processes in the elderly, such as vascular inflammation and neurotoxicity in the brain and inflammatory responses to sleep loss.

A critical dimension of basic research on chronic diseases and organ systems is the development of innovative technologies, research tools, and materials that are revolutionizing our understanding of the human body and laying the groundwork for cutting-edge therapies. Heart and vascular diseases represent only one example of many chronic diseases that benefit from technology research. Use of new, noninvasive imaging techniques in the Jackson Heart Study, a longitudinal study of heart and cardiovascular disease in African Americans in Mississippi, is expected to provide important new insights into the origins of heart disease in this population. Likewise, advances from disciplines such as materials science, tissue engineering, bioengineering, and computational sciences are providing a foundation for the development of replacements for damaged or diseased small blood vessels, from which thousands of patients with vascular disease could benefit each year.

Detecting and Diagnosing Chronic Disease

Early detection and diagnosis of a chronic disease or of damage to an organ allows patients to seek appropriate care and, in some cases, improve their outcomes or prevent progression of the disease. NIH fosters research on disease detection and diagnosis through the identification of biomarkers that predict disease or its progression, as well as the development of technologies or resources to promote early detection. For example, the NIH-supported Drug-Induced Liver Injury Network (DILIN) performs research on liver toxicity caused by prescription drugs or CAM. Among many research projects, DILIN researchers are developing better diagnostic tools and studying the mechanisms of liver injury. Related clinical research on acute liver failure from drug-induced liver injury conducted by the Acute Liver Failure Study Group has identified a potential biomarker for liver injury caused by excessive amounts of the over-the-counter pain reliever acetaminophen, which could be used clinically to aid diagnosis. In another example, the Alcohol Biosensors Program is engineering devices for the continuous measurement of alcohol concentrations that will provide new tools for clinical and basic research on alcohol use disorders.

In addition to advanced technology, the dissemination of knowledge to health care providers is one of the most important tools for disease detection and diagnosis. NIH has updated the booklet *Helping Patients Who Drink Too Much: A Clinician's Guide* to educate primary care and mental health clinicians on evidence-based methods to screen, diagnose, and manage patients who may have alcohol use disorders. In addition to traditional printed handouts and fact sheets, NIH also offers information for doctors and other health professionals in electronic formats. Two CD-ROMs, Bone Health Information for You and Your Patients and Lupus and Other Related Information for You and Your Patients, provide print-friendly PDF files of health education brochures and professional educational resources, as well as Web links to current clinical trials and other resources from Federal agencies and nonprofit organizations. Additional efforts to convey information about chronic disease detection and diagnosis to the medical community are described in the section “Health Communication and Information Campaigns and Clearinghouses” in Chapter 3.

Identifying Risk and Preventing Chronic Disease

Many chronic diseases have genetic or hereditary components that increase the risk of disease in certain individuals or population groups. Chronic diseases also may have known, modifiable risks factors such as diet, smoking, chronic stress, exposure to environmental toxins, or a variety of other factors. Often, disease results from complex and poorly understood interactions among multiple genetic, environmental, and behavioral risk factors. NIH supports research to identify all types of risk factors for chronic diseases and to develop new strategies to modify risk to prevent disease.

The completion of the Human Genome Project has opened new avenues of research into the genetic causes of chronic diseases. Diseases and conditions for which NIH-supported investigators have recently identified susceptibility genes include:

- Age-related macular degeneration, a common cause of irreversible vision loss (Age-Related Eye Disease Study)
- Inflammatory bowel disease (Inflammatory Bowel Disease Genetics Consortium)
- Alcoholism and related disorders (Collaborative Study on the Genetics of Alcoholism)
- Diabetic Kidney Disease (Genetics of Kidneys in Diabetes Study)

The datasets collected through many NIH-supported genetics studies are available, with appropriate mechanisms in place to safeguard subjects' privacy, to qualified researchers worldwide.

Ongoing initiatives such as the ENDGAME (Enhancing Development of Genome-Wide Association Methods) consortium are developing new approaches to understanding the role of genetic variation in normal physiology and disease, whereas two major ongoing studies (the Candidate Gene Association Resource and the Framingham SHARe Program) are focusing onthe genetics of cardiovascular disease. In addition, a public-private partnership led by NIH—the Genetic Association Information Network (GAIN)—is exploiting the completion of a detailed map of human genetic variation to search for genes involved with specific diseases and to develop tools to understand how environmental factors interact with genetic susceptibilities. (For more on GAIN, see the section “Genomics” in Chapter 3.)

Genetic susceptibility is rarely the only risk factor for developing a chronic disease. NIH also supports research to identify other, nongenetic risk factors that, either alone or in conjunction with genetic factors, influence the development or progression of chronic diseases. Identifying risk factors for a specific disease from the myriad behaviors and environments of individuals requires studying large numbers of people for extended periods of time. Two research studies of osteoporosis and other age-related chronic diseases—the Study of Osteoporotic Fractures and Mr. OS—have uncovered specific risk factors, such as bone mineral density of the hip, that predict the risk of fractures in the elderly. The Osteoarthritis Initiative is tracking 4,800 individuals who are at high risk for knee osteoarthritis to identify biological markers that predict disease progression. NIH-supported researchers also are investigating the complex biological and behavioral f actors underlying childhood and maternal obesity and testing behavioral interventions in schools, homes, and the community in an effort to stem the rising obesity epidemic.

Many population groups, whether stratified by race, ethnicity, sex, age, or other characteristics, seem to be particularly vulnerable to specific chronic diseases. NIH research programs that are exploring genetic and nongenetic disease risk factors in specific populations include:

- Cardiovascular disease among African Americans (Jackson Heart Study)
- Heart disease, COPD, kidney disease, and asthma in Latin Americans (Hispanic Community Health Study)

- Obesity and diabetes in the Pima Indians of Arizona (Gila River Indian Community Longitudinal Study)
- Alcohol consumption, drug use, and related disorders in various racial and ethnic groups (National Epidemiologic Survey on Alcohol and Related Conditions)
- Interdisciplinary centers on the influence of sex and gender as it relates to diseases and conditions such as chronic pain, irritable bowel syndrome, and urologic health (Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health)
- Type 1 diabetes in children (The Environmental Determinants of Diabetes in the Young)

Knowing the factors that increase or decrease the risk of disease can help researchers design innovative strategies to prevent disease in susceptible individuals. Interventions are being developed and tested to prevent trauma-related mental health disorders, such as posttraumatic stress disorder, in persons engaged in high-risk occupations such as the military or emergency response. The Diabetes Prevention Program Outcomes Study currently is assessing long-term outcomes in its subjects; the study previously had demonstrated that lifestyle change or treatment with the drug metformin significantly delayed the onset of type 2 diabetes in at-risk individuals. Lifestyle changes (modifications in diet and physical activity) were nearly twice as effective as drug treatment in reducing the risk of developing type 2 diabetes in that study. Furthermore, the physical activity increases in the lifestyle modification group were sustained for 4 years, indicating that modest changes in behavior can be accomplished and maintained for long periods. A related clinical trial, Look AHEAD (Action for Health in Diabetes), is testing whether an intensive lifestyle intervention for weight loss can reduce the incidence of cardiovascular events in 5,100 overweight or obese subjects with type 2 diabetes. Testing strategies for prevention and early treatment of type 1 diabetes is the focus of the TrialNet clinical research network. The network recently began a new clinical study of oral insulin to prevent or delay type 1 diabetes in at-risk individuals.

Prevention of chronic diseases in children is a particularly important focus of NIH research. The onset of a chronic disease in childhood often is associated with serious comorbidities (disorders or diseases in addition to the primary disease); therefore, many of these diseases, if left unchecked, have negative implications for the health of the future adult population. HEALTHY is a multicenter clinical trial testing behavioral interventions aimed at decreasing the risk of obesity and type 2 diabetes in middle school children. Likewise, the goal of the national public education outreach program Ways to Enhance Children's Activity & Nutrition (*We Can!*) is to reduce childhood obesity by helping children age 8-13 achieve and maintain a healthy weight. Asthma, another serious disease of childhood, is strongly related to environmental exposures such as indoor allergens. Researchers in North Carolina are conducting a dust mite reduction study in the homes of study subjects between ages 5 and 15 to determine whether this strategy can reduce or prevent asthma and other adverse outcomes related to dust mite exposure. The Underage Drinking Research Initiative supports multiple efforts to understand and prevent alcohol use by children and adolescents and its progression to abuse and dependence, and the Rapid Response Program supports the implementation and evaluation of programs to reduce underage alcohol use on college campuses.

NIH also sponsors awareness campaigns and other educational efforts to disseminate the results of its prevention research to the general public (see the section “Health Communications and Information Campaigns and Clearinghouses” in Chapter 3). One such campaign, The Heart Truth, takes a multifaceted approach to educate women on the risk factors for heart disease, the leading cause of death in American women.

Treating Chronic Disease and Comorbidities

Despite the remarkable advances of modern medicine, chronic diseases, by definition, require long-term medical or behavioral intervention or a combination of multiple treatment modalities. For some diseases, no effective therapies or cures are currently available, and the diseases can only be managed to control symptoms. Daily management of chronic diseases to prevent or slow the progression or development of comorbidities often imposes a significant burden on patients and their families. For example, type 1 and type 2 diabetes can be managed by injections of insulin or by taking insulin-sensitizing drugs; however, optimal control of diabetes to reduce the risk of complications also requires careful and continuous monitoring of blood glucose levels, diet, and physical activity throughout the day. A major focus of NIH research is the development and testing of new therapies for chronic disease that will cure disease, ease the process of disease management, treat patients who are not helped by current therapies, or otherwise reduce the burden of chronic illness. (For a general discussion of treatment and other clinical research, see the section "Clinical and Translational Research" in Chapter 3.) To facilitate clinical trials for many diseases, NIH supports multiple networks of investigators at medical centers across the country who can conduct studies more efficiently by working together. In addition, NIH is investing in the development of a Patient-Reported Outcomes Measurement Information System that will devise standardized measurements of symptoms that affect quality of life. Validated measures of patient-reported symptoms such as pain, fatigue, emotional distress, and others will revolutionize clinical research across a spectrum of chronic diseases and conditions.

The NIH clinical research portfolio comprises numerous trials to evaluate the safety and efficacy of therapies for many chronic diseases. The examples described here illustrate the diversity of diseases and potential therapies being studied with NIH support. Information about these and other NIH-supported clinical trials is available at http://clinicaltrials.gov.

- **Diabetes:** The long-running Diabetes Control and Complications Trial and its follow up, the Epidemiology of Diabetes Interventions and Complications study, have demonstrated that intensive insulin therapy, although not a cure for diabetes, can dramatically reduce the risk of diabetic complications of the eyes, nerves, kidneys, and heart.
- **Chronic Obstructive Pulmonary Disease (COPD):** The Long-Term Oxygen Treatment Trial is assessing the role of home oxygen therapy for patients with COPD and moderate hypoxemia (low blood oxygen level).
- **Idiopathic Pulmonary Fibrosis:** A clinical research network has been established to treat patients with newly diagnosed idiopathic pulmonary fibrosis, using combinations of drugs that might attack the fibrotic process at multiple points and thereby stabilize or improve the disease.
- **Nonalcoholic Steatohepatitis (NASH):** The NASH Clinical Research Network is investigating whether vitamin E or the drug pioglitazone is an effective treatment for nondiabetic adults with NASH, a liver disease associated with obesity and diabetes.
- **Hepatitis C:** The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial is studying whether long-term antiviral therapy can prevent the progression of liver disease in patients who have hepatitis C infection and who were not helped by short-term therapy.
- **Polycystic Kidney Disease (PKD):**The HALT-PKD trial is evaluating the use of blood pressure management in combination with medication as a means to slow progression of PKD in patients with either early or advanced disease.
- **Age-Related Macular Degeneration (AMD):** An NIH-supported trial reported in 2005 that certain vitamin and mineral supplements reduce progression of AMD, a leading cause of blindness in the elderly; the Age-Related Eye Disease Study, Part 2, is extending that result by testing additional supplements that might also slow down AMD.

- **Uveitis:** Localized steroid treatment is being testing in the Multicenter Uveitis Steroid Treatment (MUST) trial as a therapy for this major cause of blindness. If successful, this trial would improve on current treatments for uveitis that expose the entire body to corticosteroids and immune suppression drugs.
- **Ulcerative Colitis:** Many patients with ulcerative colitis do not respond to currently available treatments. A clinical trial is under way to determine whether a drug used to treat type 2 diabetes (rosiglitazone) can also control the symptoms of ulcerative colitis.
- **Drug Abuse and Addiction:** NIDA's National Drug Abuse Clinical Trials Network is a multisite research project that tests the effectiveness of new and improved behavioral, pharmacological, and integrated treatment interventions in real-life community settings with diverse populations.

Children do not always respond to treatments in the same way as adults. For this reason, NIH is committed to conducting clinical intervention trials to identify therapies that are safe and effective for use in children with chronic diseases. For example, the NASH Network (see above) is testing the use of the drug metformin or vitamin E as a treatment for fatty liver disease in children. Type 2 diabetes—a disease that was previously seen primarily in adults—is becoming more prevalent in children, and the safety of long-term use of adult diabetes drugs in children is not known. The Treatment Options for Type 2 Diabetes in Youth (TODAY) study is evaluating three strategies for treating children and adolescents with type 2 diabetes. NIH supports a multipronged approach to developing and testing therapies for asthma. The Inner-City Asthma Consortium (ICAC) evaluates immune-based therapies for asthma in inner-city children, who are disproportionately affected by the disease. At the same time, the Asthma Exacerbations: Biology and Disease Progression program is conducting basic and clinical research to facilitate development of new treatments to control asthma symptoms in children and adults.

In addition to drug development and evaluation, NIH supports research on nonmedicinal interventions for chronic diseases, including behavioral and surgical approaches. For example, researchers have developed two effective behavioral therapies—the Matrix Model and Motivational Incentives for Enhanced Drug Abuse Recovery—that help people overcome methamphetamine addiction. A clinical trial infrastructure also has been set up to facilitate testing of innovative treatments for mental disorders such as schizophrenia, bipolar disorder, and depression that include medical and/or behavioral therapies. The Health Maintenance Consortium is fostering collaboration among independent research projects aimed at promoting behavior change in areas such as diet, exercise, HIV prevention, smoking cessation, and others. Many diverse strategies are being tested for treatment of obesity, including the use of bariatric surgery. The Longitudinal Assessment of Bariatric Surgery (LABS) is evaluating the risks and benefits of bariatric surgery in obese adults, and a related observational study, Teen-LABS, is collecting data on the use of this procedure in obese adolescents.

Organ transplantation is a surgical option for some chronic diseases. Transplantation can alleviate disease, prolong survival, and improve quality of life, but the procedure carries its own risk of complications, including those caused by drugs that prevent organ rejection. Researchers are investigating the use of MRI to noninvasively monitor transplant rejection. If successful, this technology could be used by physicians to modulate drug regimens to precise levels that prevent rejection while allowing the patient's body to maintain enough immune activity to ward off infections. NIH established the Clinical Trials in Organ Transplantation program to further improve the outcome of organ transplantation. Researchers also are studying transplantation of specific organ tissues to treat disease, such as transplanting the insulin-producing islet cells of the pancreas to treat type 1 diabetes. The international Clinical Islet Transplantation Consortium is developing and conducting clinical studies that could improve this treatment approach for people with type 1 diabetes.

An important aspect of the NIH mission is to communicate the results of its research so that patients and the public can benefit from up-to-date information on treatment options (see the section "Health Communication and Information Campaigns and Clearinghouses" in Chapter 3). Sometimes this goal is accomplished through public awareness campaigns, such as one for COPD called "COPD: Learn More, Breathe Better," which distributes materials on COPD to patients, persons at risk, health care professionals, and community-level organizations to raise awareness of COPD. COPD is a disease that often goes undiagnosed, and therefore untreated, in an estimated 12 million Americans. For other diseases, translational researchers are exploring the best ways to transfer knowledge from controlled research settings into standard medical practice and the community to achieve maximum benefits for public health. Research is ongoing to find sustainable and cost-effective means to translate the successes of clinical trials for the treatment of diabetes and obesity into the real world. NIH-supported scientists also are identifying ways to promote the use of evidence-based interventions for treatment of mental illnesses.

A 2002 survey conducted by NIH and CDC found that one-third of American adults use some form of complementary and alternative medicine (CAM) to prevent or treat disease, including diverse modalities such as acupuncture, meditation, megavitamin therapy, herbs, special diets, chiropractic care, prayer, and other methods. The goal of NIH research on CAM is to provide an evidence-based assessment of the safety and effectiveness of CAM practices in order to guide and protect patients and consumers who are making treatment choices. NIH has developed a 5-year strategic plan to define priorities for CAM research, much of which pertains to a variety of organ systems and chronic diseases.

NIH-supported studies of popular dietary supplements have reported mixed results. One study showed that high doses of a form of vitamin E did not lower cholesterol in the blood, whereas in another study, glucosamine and chondroitin sulfate supplements did not relieve osteoarthritis pain in the general study population, although patients with moderate-to-severe pain did benefit. In other ongoing research, multidisciplinary teams are uncovering scientific explanations for some of the effects of acupuncture in relieving pain and are evaluating the use of this technique in patients with coronary artery disease, spinal cord injury, post-thoracotomy pain syndrome, and a number of other chronic conditions.

Addressing Pain and Palliative Care in Chronic Diseases

Pain and palliation—care to alleviate the symptoms of disease and improve quality of life—are issues associated with many chronic diseases, regardless of the organ system affected. NIH supports research to understand the origins of pain, develop therapies to manage pain effectively, and design palliative therapies to reduce suffering and improve disease outcomes. NIH is pursuing multidisciplinary approaches to the discovery of non-opioid pain medications that can selectively and safely treat chronic pain without creating drug dependence. For example, basic pharmacological research has uncovered previously unknown receptor combinations in the body that represent new targets for pain control. Nonpharmacological strategies for pain management also are being closely studied. For example, researchers have confirmed that acupuncture is an effective add-on to conventional treatment for osteoarthritis, a common cause of pain and reduced quality of life in elderly patients. The Spine Patient Outcomes Research Trial has determined which patients with back pain are most likely to benefit from surgical intervention. The Orofacial Pain: Prospective Evaluation and Risk Assessment study is seeking better ways to manage the chronic pain of temporomandibular muscle and joint disorders.

Because of the broad diversity of chronic diseases associated with pain, NIH established the NIH Pain Consortium to enhance research and promote collaboration among the many ICs that have an interest

in pain and pain management research. Since its establishment, the consortium has sponsored two symposia featuring new and exciting advances in pain research and pain management. Consortium ICs also have issued an NIH-wide research initiative to encourage pain research and delineate cross-cutting NIH interests in pain.

NIH research addresses the application of palliative care at all stages of a disease process, including at the end of life, and encompasses the needs of patients and their caregivers. Behavioral strategies have been shown to improve patient outcomes for several chronic diseases, including diabetes, irritable bowel syndrome, and asthma. Researchers also have developed a support intervention that significantly improves the quality of life for caregivers of patients with Alzheimer's disease; further research is needed to determine how best to implement this intervention through community health service networks so that more caregivers can benefit. In FY 2006, the proceedings of an NIH-sponsored State-of-the-Science Conference on Improving End-of-Life Care were published as a supplement to the *Journal of Palliative Medicine*. This special supplement reported on the state of the science in end-of-life care and proposed new research directions to improve care for all patients and their families in the final stages of disease.

Notable Examples of NIH Activity

Key for Bulleted Items:
E = Supported through **E**xtramural research I = Supported through **I**ntramural research O = **O**ther (e.g., policy, planning, or communication) COE = Supported through a congressionally mandated **C**enter **o**f **E**xcellence program GPRA Goal = Concerns progress tracked under the **G**overnment **P**erformance and **R**esults **A**ct

Understanding Fundamental Mechanisms of Organ Health and Disease

Innovative Technologies for Engineering Small Blood Vessels: NIH has initiated a program of basic research studies for the future development of replacements for damaged or diseased small blood vessels. Thousands of patients each year could benefit from small blood vessel substitutes (e.g., to bypass coronary artery or peripheral vascular occlusions or to establish arteriovenous shunts for hemodialysis), but currently available replacement grafts have a high failure rate. Recent advances in materials science, bioengineering, and tissue engineering, as well as the availability of better computational tools, are providing opportunities for the development of replacement blood vessels with properties that closely match those of natural blood vessels.

- This example also appears in Chapter 3: Molecular Biology and Basic Sciences and Chapter 3: Technology Development.
- (E) (NHLBI)

Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS): In a joint effort, NHLBI, the Center for Medicare and Medicaid Services, and FDA created INTERMACS, a national registry for patients who are receiving mechanical circulatory support device therapy to treat advanced heart

failure. Data from INTERMACS are expected to improve patient evaluation and management; aid in the development of safer, more effective devices; and enhance research.

- For more information, see http://www.uab.edu/ctsresearch/mcsd
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E) (NHLBI)

Women's Health Initiative: In January 2007, NIH awarded support for a dozen 2-year research projects to apply genomics, proteomics, and other innovative technologies to improve understanding of several major diseases that commonly affect postmenopausal women. The new endeavor builds on the long-running Women's Health Initiative, which conducted several clinical trials and an observational study to examine strategies for preventing heart disease, breast and colorectal cancers, and osteoporosis in a cohort of more than 160,000 subjects. Investigators will use stored blood, DNA, and other biological samples and associated clinical data to analyze genetic factors and biological markers that may be useful in predicting disease outcomes or the effects of therapeutic and preventive regimens in postmenopausal women.

- For more information, see http://www.whiscience.org/baa/2006.php
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics.*
- (E) (NHLBI)

Inflammation in the Elderly: Inflammatory processes, particularly those mediating chronic inflammation, have been implicated as predictors or initiators of or contributors to a number of chronic diseases and conditions of aging. NIH currently supports research to determine relationships of age-related changes in inflammation and inflammatory mediators to physiologic and pathophysiologic aging changes, risks and progression of age-related morbidity and disability, and changes in tissue and organ function. Funded projects include studies of vascular inflammation and neurotoxicity in the aging brain and inflammatory responses to sleep loss.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-05-011.html
- Heisler LK, et al. *Neuron*. 2006;51:239-49. PMID: 16846858
- Zorrilla EP, et al. *Proc Natl Acad Sci U S A* 2006;103:13226-31, PMID: 16891413
- For more information, see http://tinyurl.com/22o9mv (Obesity chapter)

Neurobiology of Appetite Control: NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. Examples include research on how serotonin reduces appetite; the actions of the protein mTOR in sensing nutrients in the body so as to modulate food intake; and a strategy to block ghrelin, a stomach-secreted hormone that signals the brain to increase food intake. This research has implications for new therapies for obesity.

- Cota D, et al. *Science* 2006;312:927-30. PMID: 16690869
- Heisler LK, et al. *Neuron* 2006;51:239-49, PMID: 16846858
- Zorrilla EP, et al. *Proc Natl Acad Sci U S A* 2006;103:13226-31, PMID: 16891413
- For more information, see http://tinyurl.com/22o9mv (Obesity chapter)
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (NIDDK)

Lymphatic System in Health and Disease: NIH recently announced two funding opportunities for research to increase understanding about the lymphatic system and its function in health and disease.

The lymphatic system plays a critical role in the well-being of many other systems in the body. When it is not working properly, a broad array of diseases and disorders can result, including lymphedema (characterized by accumulation of lymph fluid that often results in swelling of the arms or legs), inflammation and infections, cancer, and metabolic disorders. In July 2007, NIH issued the Program Announcement "Lymphatic Biology in Health and Disease" to encourage research on the biology of the lymphatic system and potential new therapeutic approaches. In addition, in December 2006, NIH re-issued the Program Announcement "Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases" to stimulate research on the lymphatic system and lymphatic dysfunction and related diseases, as well as to develop new diagnostic methods and treatment interventions.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-420.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-165.html
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (**NHLBI**, NCCAM, NCI, NIAMS, NIBIB, NICHD, NIDDK, NINR)

Understanding the Mechanisms of Alcohol-Induced Tissue Injury: Virtually every organ system of the body is impacted by heavy alcohol use (the most vulnerable being the brain and liver), and the resulting pathological conditions contribute to increased mortality and morbidity among all age and racial/ethnic groups and genders. NIH is especially interested in elucidating mechanisms of injury common to multiple body and organ systems. A number of Program Announcements and RFAs have been issued to support research to increase our understanding of the underlying cellular and molecular mechanisms of tissue injury caused by alcohol consumption, including alcohol's genetic, epigenetic, and metabolic effects. The long-term goals of these initiatives are to identify biomarkers for alcohol exposure and for the early detection of alcohol-induced tissue injury, and to develop new therapeutics that control or modify outcomes of chronic alcohol use.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-065.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-360.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-361.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-004.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-005.html
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*, Chapter 2: *Neuroscience and Disorders of the Nervous System*, and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E/I) (NIAAA)

Jackson Heart Study Advanced Imaging Component: The Jackson Heart Study is a longitudinal study of heart disease and cardiovascular disease in about 5,000 African Americans in the Jackson Mississippi area. Data collection for this study began in 2000. New imaging techniques that include dynamic MR imaging of the heart to assess cardiac function and CT imaging to assess visceral abdominal fat and calcification of the aorta and coronary vessels can provide significant additional understanding of heart disease in this minority population. NIH is in the process of adding these valuable components to the study of heart disease. The CT studies began in spring of 2007 and the MR studies are being set up now and will begin in early 2008.

- For more information, see http://www.nhlbi.nih.gov/about/jackson/index.htm
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (**NIBIB**, NCMHD, NHLBI)

Systems Biology Approach to Salivary Gland Physiology: Previous research has catalogued the genes and proteins expressed in the salivary glands. This initiative puts those catalogues into context by defining when and where genes and proteins are expressed and how they function as parts of a fully integrated biological system. The initiative combines the power of mathematics, biology, genomics, computer science, and other disciplines to translate this highly detailed information into more precise and practical leads to treat Sjõgren's syndrome, a debilitating autoimmune disorder that affects millions of Americans. The initiative also will help in learning to use saliva as a diagnostic fluid for a variety of conditions, from AIDS to cancer to diabetes.

- For more information, see http://www.nidcr.nih.gov/GrantsAndFunding/See_Funding_Opportunities_Sorted_By/ConceptClearance/ CurrentCC/SysAppySal.htm
- For more information, see http://grants2.nih.gov/grants/guide/rfa-files/RFA-DE-08-001.html
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Genomics.*
- (E) (NIDCR)

Beta Cell Biology Consortium (BCBC): The BCBC is collaboratively pursuing key challenges relevant to the development of therapies for type 1 and type 2 diabetes, including studying pancreatic development to understand how insulin-producing beta cells are made, exploring the potential of stem cells as a source for making islets, and determining the mechanisms underlying beta cell regeneration. The BCBC has generated key research resources, such as animal models, microarrays, and antibodies, which are available to the scientific community.

- For more information, see http://www.betacell.org
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Molecular Biology and Basic Sciences*
- (E) (NIDDK)

Urinary Tract Infections: NIH supports a Specialized Center of Research on Sex and Gender Factors Affecting Women's Health. This program advances new understanding of host-pathogen interactions that occur throughout the infectious cycle, including host defense response in the bladder and the virulence mechanisms by which bacterial pathogens subvert the defenses.

- Justice SS, et al. *Proc Natl Acad Sci U S A* 2006;103:19884-9, PMID: 17172451
- For more information, see http://clinicaltrials.gov/ct/show/NCT00068120
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense.*
- (E) (NIDDK)

Systems Science and Health: Solutions to complex problems like chronic disease require approaches that can address a broad range of factors within a single framework—from genetic to environmental, cellular to behavioral, and biological to social. A 2007 Symposium Series on Systems Science and Health focuses on approaches that consider how numerous factors interact nonlinearly over time in multiple feedback loops to influence health. These approaches show promise for unlocking the secrets of complex, multidimensional health problems and for transforming this knowledge into effective interventions that can fundamentally change population health.

- For more information, see http://obssr.od.nih.gov/Content/Lectures+and+Seminars/Systems_Symposia_Series/SEMINARS.htm
- (O) (**OBSSR**, CDC, FIC, NCI, NICHD, NIGMS)

Mechanisms of Action of CAM: Important and potentially promising findings from recently reported research aimed at elucidating the fundamental mechanisms of various CAM interventions include the following:

- Extracts of turmeric (a common component of Ayurvedic traditional Indian medicines and ingredient in Indian cuisine) containing compounds known as curcuminoids prevent experimental rheumatoid arthritis in an animal model.
- Green tea is widely promoted for a variety of health-related benefits. It contains a group of chemicals called catechins, one of which is known as epigallocatechin gallate (EGCG). Investigators recently reported that an EGCG-enriched extract of green tea significantly improves glucose and lipid metabolism in an animal model of obesity/insulin resistance/metabolic syndrome.

  - Funk JL, et al, *J Nat Prod* 2006;69:351-5, PMID: 16562833
  - Li RW, et al, *J Ethnopharmacol* 2006;104:24-31, PMID: 16202550
  - This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*
  - (E) (NCCAM)

Inflammatory Factor Mediates Nerve Degeneration in Glaucoma Model: In glaucoma, elevated eye pressure plays a role in damaging fibers in the optic nerve, which relays visual signals to the brain. However, the link between pressure and nerve damage is not well understood. Recent research in mice suggests a critical role for the protein TNF-a in developing glaucoma. A molecular target in the glaucoma disease pathway opens up doors for drug therapy.

- Nakazawa T, et al. *J Neurosci* 2006;26:12633-41, PMID: 17151265
- This example also appears in Chapter 2:*Neuroscience and Disorders of the Nervous System.*
- (E) (NEI)

Wound Healing and Skin Biology: Recent advances in wound healing research have brought greater understanding to skin biology, with implications for hair growth and skin diseases, as well as treatment of chronic wounds. When skin is wounded, a protein, S100A7, is released and attaches to and reduces survival of potentially disease-causing bacteria on the skin, preventing the development of wound-related infections.

- Lee KC, Eckert RL. *J Invest Dermatol* 2007;127:945-57, PMID: 17159909
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/wound_bacteria.asp
- (E) (NIAMS)

Leiomyomata Uteri (Uterine Fibroids): Some estimates suggest that uterine fibroids could affect as many as 77 percent of women nationwide and that more than 25 percent have active symptoms. NIH researchers recently found that, unlike normal uterine tissue, abnormal fibroid tissue is not affected by reproductive hormones. This suggests that the conventional hormone therapies used to treat fibroid tumors are unlikely to yield lasting improvements. Based on the findings, NIH researchers are planning studies to test two new drug treatments. One would block collagen from forming to help keep existing fibroids from growing larger; the second would help to break apart collagen fibrils in an attempt to shrink existing tumors.

- Leppert PC, et al. *Fertil Steril* 2004;82:1182-7, PMID: 15474093
- (E/I) (NICHD)

Anti-inflammation/Resolution Regulator May Be Involved in a Wide Range of Human Diseases: Resolvin E1 (RvE1) is a new family of bioactive products of omega-3 fatty acid. Using periodontitis as a model disease, a team of NIH-funded researchers recently reported that RvE1 can dramatically alter the progression of microbe-initiated local inflammatory disease. RvE1 therapy demonstrates greater efficacy without the side effects of chronic antibiotic usage. The results of their study provide new directions for treatment of localized aggressive periodontitis and other inflammation-related bone disorders. In many chronic disorders similar to periodontitis, prolonged and unresolved inflammation contributes to pathogenesis. It is now clear that several endogenous biochemical pathways activated in the host during defense reactions can counter-regulate inflammation. This study provides evidence for the role of resolvin E1 as an endogenous anti-inflammation/resolution regulator that may be involved in the pathogenesis of a wide range of human diseases.

- Hasturk H, et al. *FASEB J* 2006;20:401-3, PMID: 16373400
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCR)

New Molecular Targets to Halt Periodontal Bone Loss:: Approximately 80 percent of American adults have some form of periodontal disease. Chronic periodontitis erodes supporting structures of the tooth, leading to tooth loss. The risk of periodontal diseases is higher in smokers and individuals with diabetes; 18 million Americans suffer from diabetes and related complications, including increased incidence and severity of periodontitis. This higher incidence and severity is associated with increased cell death in bone and tissue-forming cells called osteoblasts and fibroblasts. The loss of these cells results in decreased capacity to repair tissue and bone. NIH-supported investigators published two separate papers describing the mechanisms by which the diabetic state enhances cell death. The papers suggest that d iabetes-induced cell death and compromised tissue repair are mediated by the TNF-a pro-apoptotic pathway, the major effector being caspase-3. Inhibition of TNF-a or caspase-3 activity rescues cell death and restores repair capacity. Discrimination between harmful microbes and commensal species is a critical property of the mucosal immune system, which is essential for maintaining health. Host immune cells have surface receptors that recognize bacterial species such as those known to be associated with periodontitis. Host immune cells can selectively learn to respond strongly or to tolerate endotoxin produced by recognized bacteria. NIH-supported scientists found that patients with chronic periodontitis overproduce a molecule known as SHIP, which plays an important regulatory role in signaling immune cells to tolerate endotoxin. Data from these studies suggest possible targets for developing new ways to treat or prevent chronic periodontitis.

- Al-Mashat HA, et al. *Diabetes* 2006;55:487-95, PMID: 16443785
- Liu R, et al. *Am J Pathol* 2006;168:757-64, PMID: 16507891
- Muthukuru M, Cutler CW. *Infect Immun* 2006;74:1431-5, PMID: 16428799
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NIDCR)

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

- Drug Development for Cognitive Impairments in Schizophrenia:The Treatment Unit for Research on Neurocognition in Schizophrenia program is a network that is testing the safety and efficacy of new therapeutic compounds for treating the cognitive deficits of schizophrenia.
  - (E) (NIMH)

- Studies of Fragile X Syndrome:NIH has entered into a public-private partnership to study and test possible medications for treating fragile X syndrome, the most common cause of inherited mental impairment. Fragile X syndrome is caused by a single gene mutation that ultimately results in exaggerated activity of a brain protein called mGluR5. Researchers will study, in animals, the safety of chemical compounds known to block this mGluR5 activity. If this phase goes well, researchers will move forward with clinical studies.
  - (E) (NIMH, NINDS, NICHD)

- Faster-Acting Depression Treatments:A recent NIH-funded study found that people with treatment-resistant depression experienced relief in as little as 2 hours after a single intravenous dose of ketamine, a medication usually used in higher doses as an anesthetic. Used in very low doses, ketamine is important for depression research but at higher doses could have side effects that may limit its clinical use. Nevertheless, this research could inform the development of faster- and longer-acting medications for treating depression.
  - For more information, see http://www.nimh.nih.gov/press/ketamine.cfm
  - This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research.*
  - (NIMH)

Detecting and Diagnosing Chronic Disease

Helping Patients Who Drink Too Much: A Clinician's Guide: In January 2007, NIH issued an update to its 2005 edition of this clinician's guide. Targeted to primary care and mental health clinicians, the guide presents a user-friendly, research-based approach to screening, diagnosing, and managing patients with heavy drinking and alcohol use disorders. The updated guide offers the following new resources: CME/CE credits for physicians and nurses available through Medscape; support for medication-based therapy in non-specialty settings; a new handout with strategies to help patients reduce or quit drinking; a new dedicated Web page devoted to the guide and supporting resources for clinicians and patients; and an updated PowerPoint presentation for educators and instructors. NIH has worked closely with several organizations to disseminate the guide to their memberships.

- For more information, see http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/guide.htm
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (NIAAA)

Alcohol Biosensors Program: This Advanced Research Program, modeled on DoD's DARPA (Defense Advanced Research Projects Agency) program, was developed by NIH to generate a technical solution to address the need for continuous measurement of alcohol concentrations over time in clinical and basic research on alcohol use disorders. NIH awarded five research and development contracts for alcohol biosensor development. Each research group employed a different technological approach for alcohol measurement, and all have made substantial progress in engineering commercially viable alcohol biosensors, some of which are likely to make their way to market in the next few years.

- This example also appears in Chapter 3: *Technology Development.*
- (E) (NIAAA)

Drug-Induced Liver Injury Network (DILIN):DILIN is addressing the problem of drug-induced liver toxicity, which is increasing in the United States and has serious consequences for individuals and society. This Network enables 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 disease processes. The Network has evolved into a resource on drug-induced liver toxicity for the national clinical community and the public.

- For more information, see http://dilin.dcri.duke.edu
- (E) (NIAAA)

Identifying Risk and Preventing Chronic Disease

Genome-Wide Association (GWA) Studies and Database of Genotype and Phenotype (dbGaP): In December 2006, NIH released the initial dbGaP dataset, using GWA data from the Age-Related Eye Diseases Study (AREDS), a landmark study of the clinical course of age-related macular degeneration (AMD) and cataracts. AREDS documents, protocols, and aggregated data are made available with no restrictions. To protect patient confidentiality, de-identified, individual-level patient characteristics and family data are accessible only by authorized investigators. Correlating phenotype and genotype data provides information about the genetic and environmental interactions involved in a disease process or condition, which is critical for better understanding complex diseases and developing new diagnostic methods and treatments. Using these data, recent studies have linked two genes with progression to advanced AMD. After other factors were controlled for, certain forms of the genes increased the risk of AMD progression by 2.6- to 4.1-fold; smoking and body weight further increased risk with these gene variants.

- Seddon JM, et al. *JAMA* 2007;297:1793-800, PMID: 17456821
- For more information, see http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gap
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3:*Genomics*.
- (E) (**NEI**, NIA, NLM)

Diabetes Prevention Program Outcomes Study (DPPOS): The landmark NIH Diabetes Prevention Program (DPP) clinical trial showed that lifestyle change or treatment with the drug metformin significantly delayed the development of type 2 diabetes in people at high risk. The DPPOS is a long-term follow-up study of DPP subjects that is determining the durability of the interventions in preventing disease. DPP researchers recently confirmed that a variant in a gene predisposes people to type 2 diabetes. DPP subjects at highest genetic risk benefited from healthy lifestyle changes as much or more than those who did not inherit the variant. Participants over 60 years of age responded especially well to the lifestyle intervention, showing a 71 percent risk reduction in the incidence of diabetes, compared to groups treated with metformin or standard medical advice. The lifestyle intervention had greater impact with increasing age (from age 25 to over 60); the metformin treatment had progressively less impact with increasing age.

- Florez JC, et al. *N Engl J Med* 2006;355:241-50, PMID: 16855264
- For more information, see http://tinyurl.com/24okog
- For more information, see http://tinyurl.com/295h4l
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Epidemiological and Longitudinal Studies.*

- (E) (**NIDDK**, CDC, IHS, NCMHD, NEI, NHLBI, NIA, NICHD, ORWH)

The Heart Truth: The Heart Truth, NIH's national awareness campaign for women about heart disease, continues to extend the reach of campaign messages and promotion of the Red Dress as the national symbol for women and heart disease. Hundreds of locally sponsored Heart Truth events have taken place, and more than a billion media impressions have been achieved. The Heart Truth Road Show helps subjects learn about heart disease risk factors, provides free health screenings, and disseminates educational materials. In April 2006, the campaign launched the Heart Truth Champions program to recruit health advocates and educators in local communities to increase awareness about women and heart disease. National Wear Red Day—the first Friday in February—has become an annual event when Americans wear red clothing and accessories in recognition of the importance of heart disease in women.

- For more information, see http://www.nhlbi.nih.gov/health/hearttruth
- This example also appears in Chapter 3: Health Communication and Information Campaigns and Clearinghouses.
- (E) (NHLBI)

Ways to Enhance Children's Activity & Nutrition (*We Can!*): This national public education outreach program, focusing on parents and families in home and community settings, is designed to help children 8-13 years old achieve and maintain a healthy weight. *We Can!* program materials offer tips and activities to encourage healthy eating, increase physical activity, and reduce sedentary or computer and television screen time. Many national partners and supporting organizations are promoting the *We Can!* messages and materials, and the program is being implemented in a variety of settings. In 2007, NIH began the *We Can!* city program to assist towns and cities in mobilizing their communities to prevent childhood obesity. The first three cities that will participate in the new effort have pledged to offer *We Can!* evidence-based obesity prevention programs to parents and youth in collaboration with community-based partners. In addition, each city will distribute *We Can!* tips and information to city employees.

- For more information, see http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/
- For more information, see http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=268
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (E) (**NHLBI**, NCI, NICHD, NIDDK)

National Epidemiologic Survey on Alcohol and Related Conditions (NESARC): This nationally representative survey collected comprehensive, detailed data from approximately 40,000 individuals on alcohol consumption, use of 10 categories of drugs, and symptoms of alcohol and specific drug use disorders, as well as mood, anxiety, and personality disorders. In addition to diagnostic criteria, NESARC assessed indicators of impairment and distress due to each disorder, as well as disorder-specific treatment and help seeking. Analysis of these data is ongoing and continues to provide valuable information such as prevalence and comorbidity of mental health and substance use disorders. In addition, because NESARC data include a representative sample of ethnic and racial minority populations in the United States, a better assessment of the needs of specific populations can be made. One recent study using these data examined differences in the use of alcohol treatment services across the three largest ethnic groups in America. It showed that Hispanics and African Americans with higher

levels of problem severity were less likely to have used treatment services than were Whites with problems of comparable severity, providing useful information about disparities in treatment utilization.

- Schmidt LA, et al. *Alcohol Clin Exp Res* 2007;31:48-56, PMID: 17207101
- For more information, see http://pubs.niaaa.nih.gov/publications/arh29-2/152-156.htm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation,* Chapter 3: *Epidemiological and Longitudinal Studies*, and Chapter 2: *Minority Health and Health Disparities.*
- (E/I) (NIAAA)

Osteoporosis: NIH supports several longstanding 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. Major contributions from the SOF, which began in 1986, include findings that bone mineral density of the hip is one of the best predictors of fracture for women. Recently, Mr. OS researchers identified specific lifestyle, medical, and demographic characteristics associated with low bone mass and fracture risk in older men.

- For more information, see http://www.niams.nih.gov/News_and_Events/Advisory_Council_Minutes/2006/sum01_06.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/bonemass_men.asp
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (**NIAMS**, NIA)

Childhood and Maternal Obesity: As the maternal and childhood obesity epidemic grows, 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 topics such as:

- Basic research on the physiology, psychology, and genetics of obesity in children
- Developing working definitions of the metabolic syndrome in children and adolescents
- Linking maternal obesity, reproductive health, and pregnancy to adverse health outcomes
- Behavioral intervention trials in schools, the home, and the community
  - This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
  - (E/I) (**NICHD**, NCCAM, NCI, NCMHD, NHLBI, NIDCR, NIDDK, NINR, OBSSR, ODP/ORD)

Trial to Reduce the Incidence of Type 1 Diabetes for those Genetically at Risk (TRIGR): Researchers are conducting a study to determine whether the onset of type 1 diabetes can be delayed or prevented by weaning genetically susceptible infants to Nutramigen®, a hydrolysate of cow milk protein, instead of to a standard cow milk-based infant formula. Earlier studies in animal models have shown that hydrolyzed protein diets prevented the onset of type 1 diabetes. TRIGR is the first large effort designed to ascertain whether a simple nutritional intervention during infancy can delay or prevent the onset of type 1 diabetes in children who are at high genetic risk for the disease. Enrollment for the study was recently completed, totaling more than 2,000 children from 15 countries.

- For more information, see http://www.nichd.nih.gov/research/supported/TRIGR.cfm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*

- (E) (**NICHD**, NIDDK)

HEALTHY: The HEALTHY multicenter clinical trial aims 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 three major risk factors for diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease the risks for obesity and diabetes. In the full-scale HEALTHY trial, 42 enrolled middle schools receive the intervention, which includes changes to school food service and physical education classes, behavior change, and communications campaigns. Over 80 percent of the enrolled students are from minority populations.

- For more information, see http://www.nih.gov/news/pr/aug2006/niddk-28.htm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Minority Health and Health Disparities.*
- (E) (NIDDK)

Inflammatory Bowel Disease Genetics Consortium: This consortium of researchers in the United States and Canada applies knowledge from the Human Genome Project to the identification of genetic factors influencing the development of inflammatory bowel diseases. A genome-wide screen of samples collected recently identified three new inflammatory bowel disease susceptibility genes. The identification of such genetic factors can provide key insights into disease development and targets for designing more effective therapies for inflammatory bowel disease.

- Rioux JD, et al. *Nat Genet* 2007;39:596-604, PMID: 17435756
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-011.html
- This example also appears in Chapter 3:*Genomics.*
- (E) (NIDDK)

Irritable Bowel Syndrome: Center for Neurovisceral Sciences and Women's Health: Irritable bowel syndrome is a common disorder that occurs much more frequently in females than in males. The Women's Health and Functional Visceral Disorders Center at the University of California—Los Angeles studies the role of sex-related factors in the development of irritable bowel syndrome and its response to treatment. Basic and clinical research involving patients, animal models, and functional brain imaging techniques are exploring sex differences in stress responses within the central nervous system, colon, and hormonal and immune systems. Researchers hope to identify factors that can form the basis of more effective treatment options for irritable bowel syndrome.

- For more information, see http://www.cns.med.ucla.edu
- (E) (**NIDDK**, ORWH)

Environmental Intervention in the Prevention of Asthma: Asthma is strongly related to environmental exposures. Exposure to indoor cat, dog, house dust mite, cockroach, and mold allergens is of particular concern because about 75-80 percent of children with asthma have significant allergies, which can trigger asthma, and thus these allergens have considerable medical and economic impact. Recent data have documented the ubiquity and specific levels of critical indoor allergens. In addition, a number of studies have shown that sensitization to indoor allergens (including those that derive from house dust mites, cats, dogs, rodents, cockroaches, and fungi) is a risk factor for the subsequent development of asthma. These studies include case-control studies, prospective studies, and allergen avoidance trials. Because house dust mites have been shown to be one of the strongest risk factors for persistence of asthma, an environmental intervention dust mite reduction study is under way in North Carolina.

Volunteers between the ages of 5 and 15 years who are allergic or sensitive to dust mites are being recruited for the study. A study team will visit the homes of subjects four times over a 12-month period to measure indoor dust mite levels and collect information about the home. The results of the study will provide information that will help reduce or prevent adverse health outcomes from exposure to house dust mites and other allergens.

- For more information, see http://www.niehs.nih.gov/health/topics/conditions/asthma
- (NIEHS)

Head Off Environmental Asthma in Louisiana: Nearly 20 million people, 6.5 million of them children, suffer from asthma in the United States, and minorities are disproportionately represented. NIEHS, with the National Center on Minority Health and Health Disparities (NCMHD) and others, co-funds the Head Off Environmental Asthma in Louisiana (HEAL) project to assess the impact on asthma of environmental health conditions that were caused and exacerbated by Hurricane Katrina in New Orleans children, as well as implement an intervention program to address these problems. The Project's three main goals are (1) to conduct an extensive epidemiology study to assess the nature of the environmental and psychological impacts on children in New Orleans of Hurricane Katrina and subsequent flooding; (2) to examine the genetic and environmental risk factors for asthma, including genetic susceptibility to mold toxins, and gene interactions; and (3) to design, implement, and evaluate a case management program to meet the health care needs of children with asthma in a disrupted and highly challenging environment. The project has a clear plan for informing the community of the goals, implementation, and outcomes, as well as for receiving input from the community.

- For more information, see http://heal.niehs.nih.gov
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research.*
- (**NIEHS**, NCMHD)

The Collaborative Study on the Genetics of Alcoholism (COGA): In its 18th 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) who are densely affected by alcoholism. Several genes have been identified, including *GABRA2, ADH4, ADH5,* and *CHRM2,* 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.

- For more information, see http://zork.wustl.edu/niaaa
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System,* Chapter 3: *Genomics,* and Chapter 3: *Molecular Biology and Basic Sciences*
- (E) (NIAAA) (GPRA Goal)

Look AHEAD (Action for Health in Diabetes): This multicenter NIH-led clinical trial is examining the health effects of an intensive lifestyle intervention designed to achieve and maintain weight loss over

the long term through decreased caloric intake and increased physical activity. The impact of the intervention on the incidence of major cardiovascular events will be evaluated in 5,100 overweight or obese subjects with type 2 diabetes. Look AHEAD is one of four trials that collectively address GPRA Goal SRO-6.2.

- The Look AHEAD Research Group. *Diabetes Care* 2007;30:1374-83, PMID: 17363746
- For more information, see http://tinyurl.com/2xaypk
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 2: *Minority Health and Health Disparities*
- (E/I) (**NIDDK**, CDC, NCMHD, NHLBI, NINR, ORWH)(GPRA Goal)

International Tobacco and Health Research and Capacity Building Program: Without a significant shift in worldwide smoking patterns, tobacco is projected to cause approximately 10 million deaths each year by 2025; 70 percent of this increase will occur in developing countries. To address this rising epidemic, NIH reissued the International Tobacco and Health Research and Capacity Building Program for funding in 2007. Grantees are generating a solid evidence base that can inform effective tobacco control strategies and policies. The program focuses on five critical areas: (1) epidemiology and surveillance, (2) susceptibility and risk for smoking uptake, (3) behavioral and social sciences, (4) effective interventions, and (5) policy-related research. The program also emphasizes research on determinants of youth smoking in diverse cultural and economic settings. A central goal of this program is to strengthen capacity in tobacco research in low- and middle-income nations, which advances the science and permits greater international collaboration.

- For more information, see http://www.fic.nih.gov/programs/research_grants/tobacco/index.htm.
- (E) (**FIC**, NCI, NIDA, NIDCR, ORWH)

Jackson Heart Study: The Jackson Heart Study, a large epidemiological study of cardiovascular disease among more than 5,300 African American residents of Mississippi, has been renewed through FY 2013. The project is exploring genetic, biological, and environmental factors that influence the development and course of cardiovascular disease in African Americans. It is also seeking to expand minority participation in public health and epidemiological research by providing classes and hands-on training to interested undergraduate students. Moreover, a community health education component is using data derived from the study cohort to develop and disseminate up-to-date information on reduction of risk factors, practice of healthy lifestyles, and adherence to proven risk-reducing therapies.

- For more information, see http://jhs.jsums.edu/jhsinfo
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (**NHLBI**, NCMHD)

Osteoarthritis Initiative (OAI): The OAI is a long-term effort, developed with support from private sector sponsors and with the participation of the Food and Drug Administration, to create a resource to identify and evaluate biomarkers of osteoarthritis to be used in clinical research. The OAI, which began in FY 2002, has recruited 4,800 subjects who are at high risk for knee osteoarthritis.

- For more information, see http://www.niams.nih.gov/Funding/Funded_Research/Osteoarthritis_Initiative/default.asp
- (E) (**NIAMS**, NCCAM, NCMHD, NIA, NIBIB, NIDCR, ORWH)

Genetics of Kidneys in Diabetes (GoKinD): This program facilitates investigator-driven research into the genetic basis of diabetic kidney disease through a biospecimen repository. Individuals with type 1 diabetes were screened to identify two subsets, one with clear-cut kidney disease and another with normal kidney function despite long-term diabetes. Nearly 10,000 DNA, serum, plasma, and urine samples—plus genetic and clinical data—from more than 1,700 adults with diabetes have been collected. The entire GoKinD collection is being genotyped for whole-genome association studies as part of the previously described Genetic Association Information Network (GAIN).

- Mueller PW et al. *J Am Soc Nephrol* 2006;17:1782-90, PMID: 16775037
- For more information, see http://www.jdrf.org/index.cfm?fuseaction=home.viewPage&page_id=B9C33021-1321-C834-0382E079E7865807
- This example also appears in Chapter 3:*Clinical and Translational Research* and Chapter 3: *Genomics.*
- (E) (NIDDK)

The Environmental Determinants of Diabetes in the Young: Pinpointing the environmental factors, such as infectious agents or diet, that can trigger type 1 diabetes in genetically susceptible individuals is crucial to developing prevention strategies. To address this knowledge gap, NIH established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium. This international consortium is enrolling newborns at high genetic risk and following them until age 15 to identify environmental triggers for type 1 diabetes. The study is amassing the largest set of data and samples in the world for newborns at risk for type 1 diabetes.

- For more information, see http://teddy.epi.usf.edu
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (**NIDDK**, CDC, NIAID, NIEHS)

The Gila River Indian Community Longitudinal Study: : NIH's Phoenix Epidemiology and Clinical Research Branch studies type 2 diabetes as it occurs among Pima Indians of Arizona, who have the highest prevalence of diabetes in the world. Working closely with Pima volunteers, the Branch has made substantial progress in identifying genetic, physiologic, and behavioral factors that lead to obesity and diabetes. The Branch also has facilitated improved treatment and prevention services in this community, leading to improved blood glucose control and blood pressure in Pima with diabetes. One important result is that the rate of kidney failure due to diabetes in Pima age 45 and older has declined since 1990.

- For more information, see http://intramural.niddk.nih.gov/research/labbranch.asp?Org_ID=503
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (NIDDK)

Type 1 Diabetes TrialNet: NIH is supporting this international network of investigators, clinical centers, and core support facilities that conducts research to advance knowledge about type 1 diabetes and tests strategies for its prevention and early treatment. TrialNet recently launched a clinical trial to test whether oral insulin could prevent or delay type 1 diabetes in people with a certain disease marker. The network also completed enrollment of two trials to determine whether medicines to slow the immune response could prevent further insulin-producing beta cell destruction in people newly diagnosed with type 1 diabetes. The TrialNet infrastructure is critically important for testing emerging therapies for prevention and early treatment.

- For more information, see http://www.diabetestrialnet.org/
- For more information, see www.nih.gov/news/pr/jan2007/niddk-31.htm
- (E) (**NIDDK**, American Diabetes Association, Juvenile Diabetes Research Foundation, NCRR, NIAID, NICHD)

Prevention of Trauma-Related Mental Disorders in High-Risk Occupations: NIH is supporting a research initiative to develop and test preemptive interventions to prevent trauma-related disorders, such as posttraumatic stress disorder, among occupational groups at high risk for trauma exposure, such as the military, fire fighters, police, and rescue workers.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-010.html
- This example also appears in Chapter 2: *Neuroscience ad Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIMH)

The U.S. Surgeon General's Family History Initiative: Many people see most diseases as the result of interactions of multiple genes and environmental factors. Health care professionals have known for a long time that common diseases, such as heart disease, cancer, and diabetes, and rare diseases, such as hemophilia, cystic fibrosis, and sickle cell anemia, can run in families. The U.S Surgeon General's Family History tool was created in a collaborative effort among the Office of the Surgeon General, NIH, CDC, AHRQ, and the Health Resources and Services Administration (HRSA). The U.S. Surgeon General's Family History tool (available in both English and Spanish) is free and has proven to be an effective personalized tool for individualizing preventive care and disease prevention—in other words, maintaining good health. Recently updated, this tool allows an individual to record health conditions that have affected his or her relatives. It utilizes a three-generation pedigree to gather information on health conditions in one's family to help doctors take action to keep individuals and families healthy.

- Guttmacher AE, et al. *N Engl J Med* 2004;351:2333-6, PMID: 15564550
- For more information, see http://www.hhs.gov/familyhistory
- For more information, seehttps://familyhistory.hhs.gov
- This example also appears in Chapter 3: *Genomics.*
- (O) (OD, NHGRI)

Transdisciplinary Tobacco Use Research Centers: 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.

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

Retinopathy Occurs in Middle-aged Adults Even Without Diabetes: Signs of retinopathy are common in the eyes of the elderly, particularly in those with diabetes. In the Atherosclerosis Risk in Communities (ARIC) study, African American subjects were significantly more likely to have signs of retinopathy (13 percent) compared with White subjects (5.5 percent). Among people with diabetes, 27 percent had

signs of retinopathy. Unexpectedly, retinopathy signs were also observed in 4.3 percent of people who did not have frank diabetes but tended to have elevated blood pressure. Future studies will examine whether these signs of retinopathy result from high blood pressure and whether they indicate an increased risk of systemic cardiovascular disease or predict a subsequent diagnosis of diabetes.

- Wong TY et al. *Am J Ophthalmol* 2007;143:970-6, PMID: 17399675
- For more information, see http://www.cscc.unc.edu/aric
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E/I) (**NHLBI**, NEI)

Environmental Triggers and Skin Diseases: CDC has excluded patients with eczema (also known as atopic dermatitis) from smallpox vaccination programs (in response to bioterrorism threats). There is concern of the risk of spreading vaccinia virus from the vaccine to the skin, which can cause eczema vaccinatum, an overwhelming and potentially lethal systemic infection. Researchers have learned that vaccinia virus grows much more in atopic dermatitis skin samples than in normal skin. Also, atopic dermatitis skin samples have lower levels of naturally occurring antimicrobial peptides, which could contribute to atopic dermatitis patients' susceptibility to eczema vaccinatum.

- Howell MD et al. *Immunity* 2006;24:341-8, PMID: 16546102
- (E) (**NIAMS**, NIAID)

Osteoarthritis: African Americans have a higher risk of bilateral radiographic (x ray-defined) osteoarthritis of the knee and hip than Whites. Two NIH-funded studies have revealed that mechanical stress can increase the production and release of osteoarthritis-related biomarkers. The research highlights the importance, when analyzing biomarkers, of considering the type and degree of physical activity in which patients with osteoarthritis participate.

- O'Kane JW et al. *Osteoarthritis Cartilage* 2006;14:71-6, PMID: 16188465
- Piscoya JL et al. *Osteoarthritis Cartilage* 2005;13:1092-9, PMID: 16168680
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/stress_oa_biomarker.asp
- This example also appears in Chapter 2: *Minority Health and Health Disparities.*
- (E) (COE) (**NIAMS**, NIA)

Bone Health: NIH researchers have established reference curves for bone mineral content and density in children. The early findings are now available according to age, sex, and race and can be used to help identify children with bone deficits and to monitor changes in bone in response to chronic diseases or therapies. Early study findings showed that bone minerals continue to accrue beyond the teenage years, so the study will continue as the adolescent subjects approach young adulthood. In another study, NIH scientists discovered two genes for osteogenesis imperfecta, or brittle bone disease. The genes affect how collagen, an important building block for bone, is formed. Although there is no treatment for the disorder, the findings allow researchers to test families who have lost a child to osteogenesis imperfecta for the presence of the defective genes.

- Kalkwarf HJ et al. *J Clin Endocrinol Metab* 2007;92:2087-99, PMID: 17311856
- Barnes AM et al. *N Engl J Med* 2006;355:2757-64 , PMID: 17192541
- Cabral WA et al. *Nat Genet* 2007;39:359-65, PMID: 17277775
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*

- (E/I) (**NICHD**, NIAMS, NIDCR, NCRR)

The Rapid Response Program: In April 2002, the Task Force on College Drinking released its seminal report A Call to Action: Changing the Culture of Drinking at U.S. Colleges. As part of its college focus, NIH initiated support of collaborations between university personnel who have responsibility for alcohol programs on various campuses and established researchers in college drinking to implement and evaluate programs to reduce underage alcohol use and its consequences. These programs include:

- RFA AA-03-008: "Research Partnership Awards for Rapid Response to College Drinking Problems." Five U01 (cooperative agreement) 5-year grants were awarded in December 2002.
- PAR-03-133: "Rapid Response to College Drinking Problems." Fifteen 3-year grants were awarded in June 2003.

This rapid funding mechanism (U18, cooperative agreement) supports timely research on interventions to prevent or reduce alcohol-related problems among college students. It was intended to support studies of services or interventions that could capitalize on "natural experiments" (e.g., unanticipated adverse events, policy changes, new media campaigns, campus-community coalitions, etc.). Each U18 grantee was required to partner with a U01 grantee. Together, these pairs, working with NIH Scientific Staff Collaborators, jointly design, develop, implement, and evaluate college drinking projects on their campuses.

- This example also appears in Chapter 2: Life Stages, Human Development, and Rehabilitation, Chapter 3: Epidemiological and Longitudinal Studies, and Chapter 3: Health Communication and Information Campaigns and Clearinghouses.
- (E) (NIAAA)

Underage Drinking Research Initiative: In 2004, NIH launched this ongoing 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 development. Activities and accomplishments in 2007 include:

- Provided the scientific foundation for *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking* (released March 6, 2007) and for the ongoing work of the Interagency Coordinating Committee on Preventing Underage Drinking
- Convened scientific meetings of experts, including the Underage Steering Committee, which met four times over a 2-year period; a Meeting on Diagnosis of Alcohol Use Disorders among Youth (April 2006); and a Meeting on Screening for Child and Adolescent Drinking and Alcohol Use Disorders Among Youth (June 2007)
- Issued three RFAs, including "Underage Drinking: Building Health Care System Responses" (four projects awarded in FY 2006), "Impact of Adolescent Drinking on the Developing Brain" (five projects awarded in FY 2007), and "Alcohol, Puberty and Adolescent Brain Development" (three projects awarded in FY 2007)
- Published *Alcohol Research & Health* Volume 28, Number 3, "Alcohol and Development in Youth: A Multidisciplinary Overview"
- Published a supplement of seven developmentally focused papers covering a broad range of underage drinking topics (accepted for the journal Pediatrics).
    - For more information, see http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm

- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation,* Chapter 2: *Neuroscience and Disorders of the Nervous System,* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (NIAAA)

Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs): ORWH led the development and implementation of a second round of SCORs with co-funding from five NIH institutes and FDA. The interdisciplinary nature of these research centers provides innovative approaches to advancing research on the influence of sex and gender as it relates to health and disease. Primary research areas funded include chronic pain, pregnancy, substance abuse, irritable bowel syndrome and interstitial cystitis, mental health, polycystic ovarian syndrome, and urologic health.

- For more information, see http://orwh.od.nih.gov/interdisciplinary/SCORs.html
- (E) (**ORWH**, NICHD, NIDA, NIDDK, NIMH, and NIAMS)

Gene Influences Antidepressant Response: Whether depressed patients will respond to an antidepressant depends in part on which version of a gene they inherit. Having two copies of one version of a gene that codes for a component of the brain's mood-regulating system increased the odds of a favorable response to an antidepressant by up to 18 percent, compared to having two copies of the other, more common version.

- For more information, see http://www.nimh.nih.gov/science-news/2006/gene-influences-antidepressant-response.shtml
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Genomics*
- (E) (NIMH)

Genetic Resources/Tools

Medical Sequencing: The completion of the human genome sequence, as well as genomic sequences of numerous other organisms, has already made a substantial impact on both biological and medical research. Public access to the raw data produced from these large-scale sequencing efforts has empowered many additional studies about the genomic contributions to disease. To expedite the transition from research data to medical practice, NIH supports initiatives that both drive technology that will make whole-genome sequencing affordable and produce data useful to biomedical research. Making affordable the sequencing of any individual's complete genome will allow personalized estimates of future disease risk and improve prevention, diagnosis, and treatment of disease. NIH's medical sequencing program is utilizing DNA sequencing to identify the genes responsible for rare, single-gene diseases; sequence all of the genes on the X chromosome to identify the genes involved in sex-linked diseases; and survey the range of variants in genes known to contribute to common diseases.

- For more information, see http://www.genome.gov/15014882
- This example also appears in Chapter 3: *Genomics*
- (E/I) (NHGRI)

Population Genomics, GAIN, and GEI: In February 2006, HHS announced the creation of two related groundbreaking initiatives in which NIH is playing a leading role. The Genetic Association Information Network (GAIN) and the Genes, Environment, and Health Initiative (GEI) will accelerate research on the causes of common diseases. GAIN is a public-private partnership among NIH, the Foundation for NIH, Pfizer, Affymetrix, Perlegen, the Broad Institute, and Abbott. GEI is a trans-NIH effort combining comprehensive genetic analysis and environmental technology development to understand the causes

of common diseases. Both GAIN and GEI are powered by completion of the "HapMap," a detailed map of the 0.1 percent variation in the spelling of our DNA that is responsible for individual predispositions for health and disease. Data from GAIN will help to narrow the hunt for genes involved in six common diseases. In June 2007, the first GAIN dataset, on attention deficit hyperactivity disorder, was released. GEI will provide data for approximately another 15 disorders and will develop enhanced technologies and tools to measure environmental toxins, dietary intake, and physical activity, as well as an individual's biological response to those influences.

- For more information, see http://www.genome.gov/19518664
- For more information, see http://www.genome.gov/19518663
- For more information, see http://genesandenvironment.nih.gov
- For more information, seehttp://www.genome.gov/11511175
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development.*
- (E/I) (NHGRI)

Multiplex Initiative: With the completion of the sequence of the human genome, genetic susceptibility tests that give personalized information about risk for a variety of common health conditions are now being developed and marketed. This genetic information ultimately will improve primary care by enabling more personalized treatment decisions for common diseases like diabetes and heart disease. This information also might motivate patients to change unhealthy behaviors. NIH investigators have teamed with the Group Health Cooperative in Seattle and the Henry Ford Health System in Detroit to launch a study to investigate the interest level of healthy young adults in receiving genetic testing for eight common conditions. Called the Multiplex Initiative, the study will also look at how people who decide to have the tests interpret and use the results in making health care decisions. One thousand subjects who meet the study's eligibility requirements will be offered free multiplex genetic testing. The testing is designed to yield information about 15 different genes that play roles in common diseases such as type 2 diabetes and coronary heart disease. Trained research educators will make follow-up telephone calls to help subjects interpret and understand test results, and subjects will receive newsletters to update them on new developments about the tested genes. This research should provide insights into how best to utilize the powerful tools of genomic medicine to improve health.

- For more information, see http://www.genome.gov/25521052
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Genomics.*
- (E/I) (NHGRI)

Candidate Gene Association Resource: Over the years, NHLBI has supported a number of major population studies that have collected extensive data on cardiovascular disease and its risk factors and manifestations. To increase the utility of the data for conducting genetic association studies, NIH initiated the Candidate Gene Association Resource program in FY 2006. This new resource will have the capacity to perform high-throughput genotyping for up to 50,000 subjects in cohort studies that have stored samples and data available on a wide array of characteristics (phenotypes) associated with heart, lung, blood, and sleep disorders. The linked genotype-phenotype data will form an invaluable resource for investigators seeking to identify genetic variants related to those disorders.

- For more information, see http://public.nhlbi.nih.gov/GeneticsGenomics/home/care.aspx
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Genomics.*
- (E) (NHLBI)

Enhancing Development of Genome-wide Association Methods (ENDGAME): The ENDGAME consortium, which comprises 11 interactive teams of investigators, has been initiated to explore new approaches for designing and conducting genome-wide association studies (GWAS) of complex diseases. ENDGAME investigators are developing and testing innovative, informative, and cost-effective study designs as well as analytical strategies and tools for performing the studies. All strategies and tools developed will be made available to the scientific community. Results from ENDGAME are expected to greatly enhance the utility of GWAS for increasing understanding about genetic variations and their role in health and disease.

- This example also appears in Chapter 3:*Genomics*
- (E) (**NHLBI**, NCI, NHGRI, NIEHS, NIGMS)

Framingham SNP-Health Association Resource (SHARe): The Framingham SHARe is a comprehensive new effort by NIH and the Boston University School of Medicine to pinpoint genes underlying cardiovascular and other chronic diseases. The program builds on the Framingham Heart Study, which was begun in 1948 to identify factors that contribute to cardiovascular disease, and on other NIH-funded research demonstrating that common but minute variations in human DNA, called single nucleotide polymorphisms (SNPs), can be used to identify genetic contributors to common diseases. The initiative will examine more than 500,000 genetic variants in 9,000 study subjects across three generations. NIH will develop a database to make the data available to researchers around the world. The database will help researchers integrate the wealth of information collected over the years in the Framingham study with the new genetic data, resulting in an increased understanding of genetic influences on disease risk, manifestation, and progression. Because of its uniqueness in including three generations of subjects with comparable data obtained from each generation at the same age, the Framingham Heart Study is the first study to be included in the SHARe initiative. NIH is currently considering expansion of SHARe to include other large longitudinal studies, such as the Jackson Heart Study and the new Hispanic Community Health Study.

- For more information, see http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2460
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics.*
- (E) (**NHLBI**, NLM)

Hispanic Community Health Study: In October 2006, NIH began the largest long-term epidemiological study of health and disease ever conducted in people of Latin American heritage living in the United States. The project, which will include about 16,000 subjects, is designed to identify factors that predispose individuals to develop heart disease, stroke, asthma, COPD, sleep disorders, dental disease, hearing loss, diabetes, kidney disease, liver disease, cognitive impairment, and other chronic conditions. Characteristics such as diet, physical activity, obesity, smoking, blood pressure, blood lipids, acculturation, socioeconomic status, psychosocial factors, occupation, health care access, environment, and use of medications and dietary supplements will be assessed.

- For more information, see http://www.nhlbi.nih.gov/new/press/06-10-12.htm
- 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, ODS)

Treating Chronic Disease and Comorbidities

HBO "Addiction" Documentary: NIH collaborated with Home Box Office (HBO) to create a 90-minute documentary, "Addiction," which aired on March 15, 2007. An NIH expert in the treatment of alcoholism was one of several principal spokespersons for the documentary and was featured in a supplementary broadcast on treatment advances. Several NIH grantees appeared in the documentary. A general-audience HBO book was produced to accompany the film.

- For more information, see http://www.hbo.com/addiction
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (**NIAAA**, NIDA)

Success in Treating Drug Addiction Internationally: International efforts to disseminate effective drug abuse treatments have seen success in countries with epidemic opiate addiction and/or HIV problems. Because of NIH research demonstrating that addiction is a chronic, relapsing disease that can be effectively treated, a culture change is starting to occur in these countries. For example, despite experiencing severe drug problems, Malaysia lagged behind in the treatment of drug addiction and related disorders, even as it coped with having the second-highest HIV prevalence rate among adult populations and the highest proportion of HIV cases from injection drug use. Historically, drug abusers were "rehabilitated" involuntarily in correctional facilities, and although 60 percent of prisoners had drug-related offenses, no or minimal treatment was available in prison and no medications were permitted. This primarily criminal treatment approach had limited effectiveness, which led to widespread public dissatisfaction and the recent introduction of medications for addiction. These include naltrexone (1999), buprenorphine (2001), and methadone (2003). These drug treatment programs, which were rapidly embraced by the country's medical community, have resulted in tens of thousands of opiate-dependent patients receiving medical treatment. Now the Ministry of Health, rather than the Ministry of Security, has authority for providing medical treatment for heroin addiction. This shift signals a remarkable change in Malaysian policies and approaches to addiction and an important opportunity to develop, implement, and disseminate effective treatments. A similar success story is starting to unfold in China as well.

- Mazlan M, et al. *Drug Alcohol Rev* 2006;25:473-8, PMID: 16939945
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIDA**, NIAID)

Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC): The DCCT demonstrated that intensive control of blood glucose levels reduced complications of the eyes, nerves, and kidneys in patients with type 1 diabetes. Long-term findings from the follow-on EDIC study show that intensive control lowers risk of heart disease. This research revolutionized disease management, leading to the recommendation that patients should begin intensive therapy as early as possible. EDIC recently found that recurrent hypoglycemia associated with intensive control does not affect patients' long-term cognitive function. After more than 20 years of studying this patient cohort, crucial insights continue to emerge.

- For more information, see http://www.bsc.gwu.edu/bsc/studies/edic.html
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (NIDDK)

Practical Clinical Trials: NIH has completed primary and secondary phases of several practical clinical trials that have examined treatment effectiveness for mental disorders such as schizophrenia, bipolar disorder, and depression. The infrastructure developed for each of these large multisite trials—involving more than 10,000 subjects at more than 200 sites—has forged efficient, effective, and collaborative relationships between scientists and clinicians throughout the country. To capitalize on the national networks established for the trials, NIH will fund infrastructure-only support for the platform of clinical sites and an administrative core. It is anticipated that the platform will serve as a critical foundation for supporting subject enrollment, facilitating communication among trial sites, maintaining up-to-date training in diagnosis and treatment, and providing needed administrative organization.

- For more information, see http://www.nimh.nih.gov/healthinformation/catie.cfm
- For more information, see http://www.nimh.nih.gov/healthinformation/stard.cfm
- For more information, seehttp://www.nimh.nih.gov/healthinformation/stepbd.cfm
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIMH)

Scientific Basis of the Placebo Effect: The placebo effect can be defined as the measurable, observable, or felt changes that occur during, but are not directly attributable to, a specific health intervention. It is a ubiquitous and frequently powerful phenomenon that operates in all forms of medicine, so good clinical research is designed to account for its effects as well as those of the intervention under study. Because of the power of the placebo effect, it is equally important to understand the mechanisms by which it operates and to explore how its benefits might be maximized to enhance the quality and effectiveness of all forms of health care. An ongoing NIH initiative is examining multiple aspects of the placebo effect through interdisciplinary investigations employing molecular, physiological, biochemical, immunological, genetic, behavioral, and social science approaches. This work is beginning to shed light on many facets of the placebo effect. For example, one recently published study showed that placebo-associated pain relief was correlated with activation of areas of the brain that are associated with pain relief that occurs through both innate mechanisms and with use of opioid narcotics. Other ongoing studies are examining the role and importance of the placebo effect in the relationship between patient and health care provider.

- Zubieta JK, et al. *J Neurosci* 2005;25:7754-62, PMID: 16120776
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research.*
- (E) (NCCAM)

The Scientific Basis of Acupuncture: Ongoing research on acupuncture includes a substantial portfolio of basic and translational studies employing state-of-the-art neuroimaging technology. This work is beginning to provide powerful scientific insight into the potential neurobiological mechanisms of action by which acupuncture might work. Clinical trials of acupuncture for a number of medical conditions are also under way, including studies examining (1) the potential role of traditional acupuncture as an additive/alternative treatment for the prevention of acute cardiac events in patients with coronary artery disease, (2) whether manual or electro-acupuncture contributes to neurological recovery after spinal cord injury, and 3) the efficacy of acupuncture in relieving post-thoracotomy pain syndrome (severe and persistent aching or burning pain along surgical scars in the chest).

- This example also appears in Chapter 2: Neuroscience and Disorders of the Nervous System and Chapter 3: Clinical and Translational Research.

- (E) (NCCAM)

Gene Therapy for Leber's Congenital Amaurosis (LCA): LCA is a rare, inherited retinal degenerative disease that causes severe vision loss in infancy. Although the disease is currently untreatable, NIH-funded investigators have restored vision in dogs with LCA by using gene therapy to replace defective copies of the retinal gene RPE65. Furthermore, new evidence suggests retinal activity also restores function to the brain's visual center. Investigators have recently begun to translate this promising therapy to patients with LCA.

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

Multicenter Uveitis Steroid Treatment (MUST) Trial: Uveitis, a disease that causes inflammation in middle layers of the eye, is a major cause of blindness in the United States and often requires systemic, long-term treatment with oral corticosteroids and immunosuppressants. Ideally, a local therapy impacting only the eye is preferable to systemic therapy. This comparative effectiveness trial tests a new intraocular implant therapy in patients with severe uveitis.

- For more information, see http://www.musttrial.org
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NEI)

COPD: Learn More, Breathe Better: Through its new education campaign, "COPD: Learn More, Breathe Better," NIH is raising public and professional awareness about chronic obstructive pulmonary disease (COPD). Launched in January 2007, the campaign is a cooperative effort, engaging the public, health care providers, health insurers, and researchers in improving COPD diagnosis and treatment. The campaign relies on print and radio public service announcements and printed informational materials intended for distribution to patients with COPD, persons at risk for the disease, health care professionals, and community organizations. Joining NIH in implementing this new campaign by promoting it among their constituencies are more than 20 partners, including the American Academy of Family Physicians, the American Lung Association, the American Thoracic Society, the American College of Chest Physicians, and the U.S. COPD Coalition.

- For more information, see http://www.nhlbi.nih.gov/health/public/lung/copd
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (NHLBI)

Pediatric Circulatory Support: Options for the circulatory support of pediatric patients younger than age 5 are currently limited to short-term extracorporeal devices, the use of which is often complicated by infection, bleeding, and blood clots. Recognizing the need for additional options, NIH established a program to facilitate the development of new circulatory support systems for infants and children with congenital or acquired cardiovascular diseases. The program supports five research groups developing a variety of devices for different pediatric applications. The common objective for the devices is to provide reliable circulatory support for infants and children while minimizing adverse effects.

- For more information, see http://grants.nih.gov/grants/guide/notice-files/NOT-HL-03-004.html
- This example also appears in Chapter 3: *Technology Development.*
- (E) (NHLBI)

Sildenafil for Pulmonary Hypertension in Adult Patients with Sickle Cell Disease: In 2006, NIH began a new study to evaluate a course of treatment with sildenafil in patients with sickle cell disease who have pulmonary hypertension. A randomized, double-blind, placebo-controlled, Phase II clinical trial is testing the drug's safety and efficacy in improving exercise capacity, symptoms, and measures of circulatory function. The trial involves approximately 180 patients at extramural sites and at the NIH Clinical Center. Because pulmonary hypertension occurs frequently in persons with sickle cell disease and confers a high risk of death, a positive outcome of this trial would represent an important step toward improved patient care.

- For more information, see http://www.clinicaltrials.gov/ct2/show/NCT00492531?term=sildenafil&rank=7
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research.*
- (E/I) (NHLBI)

Monitoring Organ Rejection Using MRI: Organ transplants give patients a new lease on life. However, preventing their immune systems from rejecting the transplanted organ sometimes presents a challenge. Physicians must strike a balance between suppressing the immune system so that it does not reject the organ and maintaining enough immune activity to ward off infections. Tracking how the body accepts the new organ is critical to this process. The current "gold standard" for monitoring organ rejection is tissue biopsy, an invasive procedure in which a physician removes a small sample of the transplanted organ for testing. Biopsy has two drawbacks: patient discomfort (the physician must perform the procedure multiple times) and poor selectivity (biopsy removes tissue from only a limited number of sites and can miss rejection starting elsewhere in the organ). To overcome these limitations, NIH-supported researchers are developing a new method to monitor organ rejection with MRI. They label macrophages (immune cells) with polymer-coated, micron-sized iron oxide particles. These magnetic particles allow the migration of the macrophages to rejection sites in the transplanted organ to be clearly tracked by MRI. At present, this work is being performed on rats, but the investigators are extending it to large animals and humans. If successful, the approach could be used to optimize the administration of immunosuppressant drugs in clinical situations.

- Wu YL, et al. *Proc Natl Acad Sci U S A* 2006;103:1852-7, PMID: 16443687
- For more information, see http://www.nibib.nih.gov/HealthEdu/eAdvances/25Sep06
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIBIB)

Asthma Exacerbations—Biology and Disease Progression: 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 symptoms. Twelve projects have been funded under this initiative. As part of NIH GPRA reporting activity, 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: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (**NHLBI**, NIAID) (GPRA Goal)

Long-Term Oxygen Treatment Trial (LOTT): Although oxygen therapy is known to benefit patients with COPD who experience severe hypoxemia (low blood oxygen level) when resting, the value of this treatment in 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 these patients and to provide a basis for Medicare coverage decisions. The LOTT trial is the focus of a new NIH GPRA goal to be included in GPRA reporting in 2007: "by 2012, assess the efficacy of long-term oxygen treatment in patients with COPD and moderate hypoxemia."

- For more information, see http://www.jhucct.com/lott/
- For more information, see http://www.nhlbi.nih.gov/new/press/06-11-20.htm
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NHLBI) (GPRA Goal)

Programs to Accelerate Medication Development for Alcoholism Treatment: Alcoholism is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ from one drinker to another. 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 their 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 have already produced several targets for human studies that are now under way, such as rimonabant, a cannabinoid CB1 receptor blocker, and antalarmin, a corticotropin-releasing factor receptor blocker.
- 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 human trials network.
  - 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 Goal)

Improving Transplantation Outcomes: Organ transplantation prolongs survival and improves quality of life for children and adults with a wide range of diseases. Yet despite advances in organ transplantation, organ recipients rarely achieve normal life expectancy and health-related quality of life. To improve the outcome of organ transplantation, NIH supports the Clinical Trials in Organ Transplantation (CTOT) initiative, a cooperative, multisite consortium that conducts interventional and observational clinical studies, as well as studies of the mechanisms of graft rejection. The consortium includes 34 clinical sites and 30 immunology laboratories at 13 universities. Five clinical trials are currently enrolling individuals undergoing kidney, heart, liver, or lung transplantation.

- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (**NIAID**, NHLBI, NIDDK) (GPRA Goal)

Blending Initiative: Bench to Bedside to Community: Efforts to systematically move science-based interventions and practices into community settings are exemplified in the testing of drug abuse

treatment approaches directly in the community settings where they will be used by drug treatment professionals who are trained to implement them. This work is occurring through the National Drug Abuse Treatment Clinical Trials Network at NIH, which involves practitioners from community treatment programs not only in formulating research protocols, but also in providing real-world feedback on their success and feasibility. The adoption of the addiction medication buprenorphine by a growing number of community treatment programs treating patients with opioid addiction is an example of real culture change issuing from NIH clinical research. A similar approach is under way to enhance treatment for drug-addicted individuals involved with the criminal justice system through research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) initiative. It seeks to achieve better integration of drug abuse treatment for criminal offenders with other public health and public safety forums and is a collaborative effort by NIH and multiple Federal agencies and health and social service professionals. These initiatives are helping to change the culture of how drug abuse treatment is delivered in this country.

- For more information, see http://www.drugabuse.gov/CTN
- For more information, see http://www.cjdats.org
- For more information, see http://www.drugabuse.gov/Blending
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System,* Chapter 3: *Clinical and Translational Research*, and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (NIDA) (GPRA Goal)

Treatments to Fight Methamphetamine Addiction: The abuse of methamphetamine—a potent and highly addictive psychostimulant—is a serious problem in the United States. Methamphetamine abuse can have devastating medical, psychological, and social consequences. Adverse health effects include memory loss, aggression, psychotic behavior, heart damage, and abnormal brain function. Methamphetamine abuse also contributes to increased transmission of hepatitis and HIV/AIDS and can spawn increased crime, unemployment, and other social ills. The good news is that methamphetamine abuse and addiction are treatable, and people do recover. As methamphetamine abuse has increased, so has NIH's support of research to combat it, including research on genetics, brain development, and translation of findings. This research has led to the development of two effective behavioral therapies for methamphetamine addiction: (1) the Matrix Model, consisting of a 16-week program that includes group and individual therapy and addresses relapse prevention, behavioral changes, establishment of new drug-free environments, and other issues; and (2) Motivational Incentives for Enhanced Drug Abuse Recovery, a cost-effective incentive method for cocaine and methamphetamine addiction that has been shown to sustain abstinence in twice the number of subjects engaged in treatment as usual. Increasingly, community treatment providers nationwide are implementing motivational incentives as part of drug addiction treatment.

- For more information, see http://www.drugabuse.gov/ResearchReports/Methamph/Methamph.html
- For more information, see http://www.drugabuse.gov/Testimony/6-28-06Testimony.html
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIDA)

Nonalcoholic Steatohepatitis (NASH) Clinical Research Network: : NASH is strongly associated with obesity and type 2 diabetes, conditions that have increased dramatically in recent decades. Network research addresses GPRA Goal SRO-4.3. The Network is conducting a randomized clinical trial to

evaluate the safety and efficacy of the insulin-sensitizing drug pioglitazone or vitamin E compared to placebo for the treatment of non-diabetic adults with NASH. Also, in a separate trial in children, the Network is comparing the insulin-sensitizing drug metformin, vitamin E, and placebo in treating nonalcoholic fatty liver disease.

- For more information, see http://www.jhucct.com/nash
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (**NIDDK**, NCI, NICHD) (GPRA Goal)

Age-Related Eye Disease Study, Part 2 (AREDS2): Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly in the United States and will be an increasing burden in future years, based on demographics. The original AREDS study, completed in 2005, demonstrated that antioxidant vitamin and mineral supplements reduced the progression to advanced AMD by 25 percent. Building on these landmark findings, AREDS2 is assessing additional supplements (lutein, zeaxanthin, and long-chain omega-3 fatty acids) as a treatment for AMD and cataracts. AREDS2 is also evaluating the effects of eliminating beta-carotene and/or reducing zinc in the original AREDS formulation on AMD progression. AREDS2 investigators will also explore gene-environment interactions in the development of these conditions, cognitive function, and cardiovascular health.

- For more information, see http://public.drcr.net
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (**NEI**)

Diabetic Retinopathy Clinical Research Network (DRCR.net): Diabetes, a leading cause of blindness in working-age adults, causes blood vessels in the retina to leak and can lead to retinal detachment. Laser treatment is effective but is not optimal. DRCR.net is a collaborative, nationwide, public-private network of eye doctors and investigators in 165 clinical sites conducting clinical research of diabetes-induced retinal disorders (diabetic retinopathy and diabetic macular edema) with the aim of evaluating promising new therapies. DRCR.net serves as a model network to provide the infrastructure to facilitate multiple concurrent and consecutive clinical trials of innovative therapies, to rapidly develop and initiate new protocols, and to interact with industry partners while ensuring scientific rigor and high ethical standards.

- For more information, see http://public.drcr.net
- This example also appears in Chapter 3: *: Clinical and Translational Research.*
- (E) (NEI)|

Comprehensive Sickle Cell Centers (CSCCs): The CSCCs were established in 1972 in response to a Presidential initiative and a Congressional mandate to support multidisciplinary research to expedite the development and application of new knowledge for improved diagnosis and treatment of sickle cell disease. In addition to basic research, training, and patient services activities, the CSCCs currently support multicenter Phase II trials, neurocognitive and neuroimaging studies, development of a collaborative database, and a study on the epidemiology of priapism (painful, prolonged erection) among patients with sickle cell disease. Ten centers are funded through FY 2007, and the program will be renewed in FY 2008.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-06-008.html
- For more information, see http://www.sicklecell-info.org
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research.*

- (E) (NHLBI)

Improving the Lives of Asthmatic Children in the Inner City: The NIH Inner-City Asthma Consortium (ICAC) evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children, who are disproportionately affected by asthma. An ICAC longitudinal birth cohort study involving 500 inner-city children is investigating the immunologic causes of the development of recurrent wheezing, a surrogate marker for asthma in children younger than age 3. The ICAC is also conducting a multicenter trial to evaluate the safety and efficacy of Xolair (omalizumab) in children with moderate to severe allergic asthma whose symptoms are inadequately controlled with inhaled steroids. Finally, researchers are conducting a clinical trial to determine the safety and dosing levels of a potential new allergy immunotherapy for cockroach allergen, which previous ICAC findings showed are a major determinant of asthma severity among inner-city children.

- This example also appears in Chapter 3: Clinical and Translational Research and Chapter 3: Epidemiological and Longitudinal Studies.
- (E) (NIAID)

Dialysis Access Consortium: Arteriovenous fistulas and grafts are the two most common methods of gaining repeated access to the circulation of patients on hemodialysis. The Dialysis Access Consortium (DAC) is conducting two trials to assess the impact of anticlotting reagents in preventing early failure in arteriovenous fistulas and grafts. The Arteriovenous Fistula Trial is evaluating the ability of clopidogrel to maintain access patency, while the Arteriovenous Graft Trial is evaluating the ability of aspirin combined with extended-release dipyridamole to maintain access patency.

- Dember LM et al. *Clin Trials* 2005;2:413-22, PMID: 16317810
- Dixon BS et al. *Clin Trials* 2005;2:400-12, PMID: 16317809
- For more information, see http://www.niddk.nih.gov/patient/dac/DAC.htm
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NIDDK)

Inflammatory Bowel Disease: Randomized Trial of Rosiglitazone for Ulcerative Colitis: Current treatments for ulcerative colitis, a form of inflammatory bowel disease, are not effective for all patients. NIH-supported scientists demonstrated that rosiglitazone, a medication used to treat type 2 diabetes, reduced inflammation in an animal model of ulcerative colitis. Subsequently, a small clinical study showed that rosiglitazone was effective in controlling ulcerative colitis symptoms. NIH is now supporting a full-scale clinical trial of this potential new therapy for ulcerative colitis.

- For more information, see http://clinicaltrials.gov/show/NCT00065065
- (E) (NIDDK)

Longitudinal Assessment of Bariatric Surgery (LABS): The multicenter, NIH-funded LABS consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Because bariatric surgery is also sometimes used in clinical practice as a treatment for severely obese adolescents, NIH is also 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.

- For more information, see http://tinyurl.com/399zmt
- For more information, see http://tinyurl.com/yoer3l
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Clinical and Translational Research.*

- (E) (**NIDDK**, ORWH)

Polycystic Kidney Disease (PKD): The Consortium for Radiologic Imaging Studies of PKD (CRISP) showed that MRI could accurately track structural changes in the kidneys of people with the more common form of PKD. An extension, CRISP II, will continue to monitor these patients to determine whether these changes in kidney volume predict changes in kidney function. NIH is also conducting two clinical trials of people with the most common form of PKD; one is in patients with early kidney disease and another is in patients with more advanced disease. These two trials are the largest multicenter studies of PKD conducted to date and are collectively termed HALT-PKD. They are testing whether optimum blood pressure management, in combination with medication, will slow the progression of PKD.

- Grantham JJ, et al. *N Engl J Med* 2006;354:2122-30, PMID: 16707749
- For more information, see http://tinyurl.com/2qu94j
- For more information, see http://www.pkd.wustl.edu/pkd-tn/
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (NIDDK)

Stress Incontinence Surgical Treatment Efficacy (SISTEr) Trial: The first of several studies to be conducted by the NIDDK-funded Urinary Incontinence Treatment Network, the SISTEr trial recently showed that the sling surgical procedure helps more women achieve dryness than the Burch surgical technique. Two years after surgery, 66 percent of women who had the sling procedure and 49 percent who had the Burch were continent.

- Albo ME et al. *N Engl J Med* 2007;356:2143-55, PMID: 17517855.
- For more information, see http://www.nih.gov/news/pr/may2007/niddk-21.htm
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NIDDK)

Studies of Diabetes in Youth: Previously known as a disease of adults, type 2 diabetes is increasingly being observed in youth. The Treatment Options for Type 2 Diabetes in Youth study is comparing three different treatment strategies for children with the disease. The SEARCH for Diabetes in Youth Study is providing key data on childhood diabetes incidence and prevalence. SEARCH estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. While type 2 diabetes is increasing in children over age 10, particularly minorities, type 1 diabetes accounts for most new cases, with an estimated 15,000 youths diagnosed annually.

- For more information, see http://www.todaystudy.org/index.cgi
- For more information, see http://www.searchfordiabetes.org
- This example also appears in Chapter 3: *Clinical and Translational Research,* Chapter 3: *Epidemiological and Longitudinal Studies,* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (**NIDDK**, CDC)

The Clinical Islet Transplantation Consortium: The purpose of this international consortium is to develop and implement a program of single- and/or multicenter clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. Research pursued through this consortium aims to make improvements in the field of islet transplantation and to share the data and results with the broad scientific community.

- For more information, see www.isletstudy.org
- (E) (**NIDDK**, NIAID)

Translational Research for the Prevention and Control of Diabetes and Obesity: NIH is supporting research projects to explore ways to bring knowledge from successful clinical research into medical practice and community settings. Studies are seeking to develop effective, sustainable, and cost-effective methods to prevent and treat type 1 and type 2 diabetes and obesity in clinical health care practice and other real-world settings. Many of these studies focus on minority populations disproportionately burdened by type 2 diabetes and obesity.

- 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)

Maintenance of Long-Term Behavioral Change: Behavioral factors contribute to the development and outcomes of many chronic diseases. Successful prevention of and treatment for chronic diseases depend, in part, upon the sustained maintenance of behavior change over time. This initiative supports research projects that examine biopsychosocial processes and test interventions designed to achieve long-term health behavior change. Funded projects focus on diet, physical activity, HIV prevention, smoking cessation, drug abstinence, suicide prevention and mammography screening. In addition, A Health Maintenance Consortium (HMC) comprising NIH program staff, research investigators at the individual sites, and representatives from cosponsoring private foundations has been established to explore the opportunities for further collaboration across the studies.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-OB-03-003.html
- For more information, see http://obssr.od.nih.gov/Content/Research/Request_for_Applications_%28RFAs%29/Behavioral+Change+RFA+Outcome.htm
- For more information, see http://hmcrc.srph.tamhsc.edu/default.aspx
- (E) (**OBSSR**, NCI, NEI, NIA, NIAAA, NICHD, NIDA, NIDDK, NIMH, NINR, ODP/ORD)

Patient-Reported Outcomes Measurement Information System (PROMIS): This NIH Roadmap initiative is developing ways to measure symptoms—such as pain, fatigue, physical functioning, social-role participation, and emotional distress—that influence quality of life across numerous chronic diseases.

- For more information, see http://www.nihpromis.org/default.aspx
- For more information, see http://www.niams.nih.gov/News_and_Events/Announcements/2007/PROMIS_supp.asp
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems.*
- (E) (Roadmap—all ICs participate) (GPRA Goal)

Comprehensive Review of Meditation Research: A recent comprehensive literature review on meditation research included more than 800 studies of a variety of forms of meditation for a number of chronic conditions, including hypertension, coronary artery disease, and substance abuse. The review concludes that there are promising indications that meditation may have beneficial effects on a variety of outcomes, including blood pressure, perceived stress, anxiety, and behavioral modification, but additional and higher-quality research is needed.

- For more information, see http://www.ahrq.gov/clinic/tp/medittp.htm

- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NCCAM)

Mind-Body Medicine: NIH supports a substantial portfolio of multidisciplinary clinical, translational, and basic research on mind-body interventions, such as meditation and Tai Chi Chuan. This effort is based on (1) promising findings from preliminary controlled clinical investigations and (2) laboratory evidence suggesting that these interventions often involve or invoke well-known biological mechanisms that are known to play key roles in the cause of and recovery from illness and in the preservation of health and wellness. For example:

- Investigators recently demonstrated that patients who practiced Tai Chi Chuan, a form of moving meditation based on traditional Chinese medicine, experienced significant augmentation in levels of immunity to the virus that causes shingles after vaccination against the virus.
- Other investigators have demonstrated that patients with chronic heart failure show improvements in quality of life, exercise ability, and biomarkers of cardiac health when Tai Chi Chuan is added to conventional medical care.
  - Irwin MR, et al. *J Am Geriatr Soc* 2007;55:511-7, PMID: 17397428
  - Yeh GY, et al. *Am J Med* 2004;117:541-8, PMID: 15465501
  - (E) (NCCAM)
  - This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences.*

Research on Popular Dietary Supplements: A significant body of research on CAM practices focuses on documenting the safety and efficacy of various widely used dietary supplements. Important recently reported findings include the following:

- The combination of glucosamine plus chondroitin sulfate did not provide significant relief of pain from osteoarthritis of the knee in the overall study population, although a subset of the study subjects with moderate-to-severe pain showed significant relief with the combined supplements.
- The dietary supplement alpha-tocopherol (a form of vitamin E), administered at a high dosage of 1,200 IU/day for 2 years, had no effect on serum concentrations of total, low-density lipoprotein, or high-density lipoprotein cholesterol.
  - Clegg DO, et al. *N Engl J Med.* 2006;354:795-808, PMID: 16495392
  - Singh U, et al. *Clin Chem.* 2007;53:525-8, PMID: 17234730
  - This example also appears in Chapter 3: *Clinical and Translational Research.*
  - (E) (**NCCAM**, NIAMS, ODS)

Losartan Offers Promise for the Treatment of Marfan Syndrome: New research offers hope that losartan, a drug commonly prescribed to treat hypertension, might also be used to treat Marfan syndrome, a genetic disorder that often causes life-threatening aortic aneurysms. After discovering that Marfan syndrome is associated with a mutation in the gene encoding fibrillin-1, researchers tried for many years, without success, to develop treatment strategies that involved repair or replacement of fibrillin-1. A major breakthrough occurred when NIH-funded researchers discovered that one of the functions of fibrillin-1 is to bind to another protein, TGF-beta, and regulate its effects. After careful analyses revealed aberrant TGF-beta activity in patients with Marfan syndrome, researchers began to concentrate on treating the disease by normalizing the activity of TGF-beta. Losartan, which is known to affect TGF-beta activity, was tested in a mouse model of Marfan syndrome. The results showed that the

drug blocked the development of aortic aneurysms as well as lung defects associated with the disease. Based on the promising results, the NHLBI Pediatric Heart Network, in partnership with the National Marfan Foundation, began a clinical trial in 2007 to assess losartan therapy in patients with Marfan syndrome.

- Habashi JP, et al. *Science* 2006;312:117-21, PMID: 16601194
- For more information, see http://clinicaltrials.gov/show/NCT00429364
- For more information, see http://www.pediatricheartnetwork.org
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NHLBI)

Acute Liver Failure Study Groups: The adult and pediatric Acute Liver Failure Study Groups address the problem of acute liver failure due to drugs or other factors. The groups' research has provided knowledge and tools for managing the clinical and public health burden of acute liver failure. In 2002, the adult Study Group highlighted a dramatic increase in liver injury due to the over-the-counter pain reliever acetaminophen. The groups then developed a serum-based assay to detect acetaminophen-induced acute liver failure in adults and children. Current studies are testing potential therapies to improve survival in patients with acute liver failure.

- Ostapowicz G et al. *Ann Intern Med* 2002;137:947-54, PMID: 16950959
- For more information, see http://tinyurl.com/2qu94j
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (**NIDDK**, FDA)

Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial: The HALT-C trial studies whether long-term antiviral therapy can prevent the progression of liver disease in people with hepatitis C who do not respond to standard, short-term therapy. The trial has advanced understanding of the impact of disease severity and antiviral drug dose on response to long-term therapy and yielded a new tool to monitor treatment response. These advances can help health care providers to determine which patients are unlikely to respond to long-term antiviral therapy, so that those patients can be spared from ineffective treatment and its side effects.

- Morishima C et al. *Hepatology* 2006;44:360-7, PMID: 17241864
- For more information, see http://www.haltctrial.org
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (**NIDDK**, NCI, NIAID)

Multidisciplinary CAM Research: Investigators are utilizing increasingly sophisticated, multidisciplinary, bedside-to-bench and bench-to-bedside approaches to elucidate the efficacy, safety, and mechanisms of action of a wide variety of CAM practices. Ongoing research encompasses virtually all organ systems and medical and scientific disciplines, as well as numerous CAM modalities and practices spanning the four major CAM domains (biologically based practices, manipulative and body-based practices, energy medicine, and mind-body medicine), as well as the alternative whole medical systems of which they are a part. Guided by its 5-Year Strategic Plan, recommendations of the National Advisory Council for Complementary and Alternative Medicine, the plans of other ICs, and input from expert panels and various stakeholders, NCCAM establishes priorities to fill gaps in the CAM research portfolio, capitalize on emerging opportunities, and leverage resources.

- For more information, see http://nccam.nih.gov/about/plans/2005/strategicplan.pdf
- For more information, see http://nccam.nih.gov/research/priorities/index.htm#5

- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NCCAM)

Advancing Novel Science in Women's Health Research (ANSWHR): In FY 2007, NIH published two Program Announcements for a new grants program called Advancing Novel Science in Women's Health Research (ANSWHR). Both announcements are intended to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex and gender differences.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-07-381.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAS-07-382.html
- (E) (ORWH, NCI, NEI, NHLBI, NHGRI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDCD, NIDCR, NIDA, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM, FIC, NCCAM, OBSSR, and ODS)

Research Enhancement Awards Program (REAP): NIH successfully implemented a trans-NIH Research Enhancement Awards Program (REAP) in both FY 2006 and FY 2007 by awarding a total of more than $6.8 million dollars. Sixteen grants were awarded in each fiscal year. This program is directed at meritorious grants that have just missed the IC pay line that will advance research on women's health and/or the study of sex and gender factors. Scientific areas covered by these grants include diabetes, fibromyalgia, genetic studies of ovarian failure, health disparities, heart failure evaluation in postmenopausal women, HIV/AIDS, interstitial cystitis, lupus, neuroendocrine development, pain control, rheumatoid arthritis, smoking in pregnancy, substance abuse, and breast cancer and CAM.

- (E) (ORWH)

Trans-NIH Chronic Fatigue Syndrome Research: NIH coordinates chronic fatigue syndrome research through the trans-NIH Working Group on Research on Chronic Fatigue. This working group developed an action plan to enhance the status of chronic fatigue syndrome research at NIH and among the external and intramural scientific communities. The working group held a workshop on grantsmanship in FY 2007 to provide researchers with an overview of funding opportunities, an understanding of the NIH funding process, and an opportunity to meet with program officials. In addition, the Office of Research on Women's Health and a subset of the working group ICs issued an RFA in FY 2006 to explicate how the brain, as the mediator of the various body systems involved, fits into the schema for understanding chronic fatigue syndrome. This RFA solicited proposals from multidisciplinary teams of scientists to develop an interdisciplinary approach to the study of chronic fatigue syndrome in men and women across the lifespan and resulted in seven new research projects on chronic fatigue syndrome.

- For more information, see http://orwh.od.nih.gov/cfs.html
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-002.html
- For more information, see http://orwh.od.nih.gov/cfs/2006NIHfundedCFSstudies.html
- For more information, see http://orwh.od.nih.gov/cfs/cfsFundingGMWs.html
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (**ORWH**, NIAID, NIAMS, NIAAA, NIA, NICHD, NIDA, NIDDK, NINDS, NCRR, CSR, NIEHS, NIDCR, NINR, NHLBI, NIMH, NCCAM, FIC, ODS, OBSSR)

Research to Strengthen the Dissemination and Implementation of Evidence-Based Mental Health Interventions: NIH continues to support research designed to strengthen the dissemination and implementation of evidence-based mental health practices. NIH released a Program Announcement to encourage transdisciplinary teams of scientists and practice stakeholders to work together to deveop innovative approaches for identifying and overcoming barriers to the adoption of evidence-based

interventions. This Program Announcement also serves as the basis for a GPRA Goal. NIH also supports research designed to enhance implementation by providing evidence of intervention benefits not just to the individual, but to a broader system as well. For example, a recent study reported that providing a minimal level of enhanced care for employees' depression would result in significant savings to employers.

- Wang PS et al, *Arch Gen Psychiatry* 2006;63:1345-53, PMID: 17146009
- For more information, see http:grants.nih.gov/grants/guide/pa-files/PAR-07-086.html
- For more information, see http://www.nimh.nih.gov/press/cost-benefitsimulation.cfm
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (I/E) (**NIMH**, NCI, NIDA, NIDCD, NINR, NIAAA, NIDCR, NIDDK, NICHD) (GPRA)

Addressing Pain and Palliative Care in Chronic Diseases

Improving End-of-Life Care: Special Supplement to the *Journal of Palliative Medicine:*: In FY 2005, NIH sponsored the State-of-the-Science Conference on Improving End-of-Life Care. This conference addressed the current state of end-of-life care and proposed important new directions for end-of-life research. Key conclusions to emerge from the conference included: the rapid increase in older adults facing the need for end-of-life care requires the development of research infrastructure to better examine end-of-life issues; enhanced communication between patients, families, and providers is crucial to end-of-life care; and improved outcome measures are needed to better conduct end-of-life research. In FY 2006, a special issue of the *Journal of Palliative Medicine* presented a series of papers developed from this workshop on a wide variety of topics. The supplement includes articles on measuring end-of-life care outcomes; analyzing racial, cultural, and ethnic factors that influence end-of-life care; improving care for dying children and their families; and examining factors in the health care system that influence end-of-life care.

- Grady PA. *J Palliat Med* 2005;8:S1-3, PMID: 16499457
- For more information, see http://www.liebertonline.com/toc/jpm/8/supplement+1
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (NINR)

Promising Approaches to Treating Chronic Pain: Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can produce drug dependence. Thus, an area of enormous need is the development of potent non-opioid analgesics, for which NIH has implemented an aggressive and multidisciplinary research program. Many of these initiatives are yielding tangible results that stand to revolutionize the field of pain management. At the molecular level, cannabinoid research has shown that it is possible to selectively activate the cannabinoid system to provide analgesia with minimal or no psychotropic side effects or abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different receptors, the targeting of which could provide a vastly expanded range of pharmacotherapeutic effects. 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 a non-neuronal brain cell type, glia, has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their pro-inflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of 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.

- For more information, see http://www.nida.nih.gov/whatsnew/meetings/painopioides
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (**NIDA**, NINDS)

Resources for Enhancing Alzheimer's Caregiver Health II (REACH II): Family members and friends who care for people with dementia face a variety of challenges that can seriously compromise their own well-being. Investigators have found that a personalized intervention consisting of home visits, structured telephone support sessions, and telephone "check-ins" can significantly improve the quality of life for caregivers of Alzheimer's disease patients. The study is the first randomized, controlled trial to look at the effectiveness of an Alzheimer's disease caregiver support intervention for ethnically diverse populations. Follow-up studies are needed to examine how this intervention might be used through existing community health service networks.

- For more information, see http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20061120caregiverQOL.htm
- (E) (**NIA**, NINR)

NIH Pain Consortium: The aims of the NIH Pain Consortium are to enhance pain research and promote collaboration among researchers across the many NIH Institutes and Centers that have programs and activities addressing pain. The consortium held its second annual symposium, Advances in Pain Research, on May 1, 2007, to feature new and exciting advances in pain research and pain management. Topics included neuropathic pain, visceral pain, inflammatory pain, and treatment-induced pain. Topics included NIH and extramural scientific communities, health care providers, and the public. Consortium ICs also issued an NIH-wide Funding Opportunity Announcement, "Mechanisms, Models, Measurement, and Management in Pain Research," to encourage pain research and delineate cross-cutting NIH interests in pain.

- For more information, see http://videocast.nih.gov/PastEvents.asp
- For more information, see http://painconsortium.nih.gov/index.html
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (**NIDCR**, CC, FIC, NCCAM, NCI, NCRR, NIA, NIAAA, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIGMS, NIMH, NINDS, NINR, OBSSR, OD, ODP/ORD, ORWH, OTT)

Behavioral Strategies to Improve Quality of Life and Chronic Disease Outcomes: As health care advances continue to transform previously acute 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 the 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 to develop and test, by 2012, at least two behavioral strategies for the management of symptoms to reduce the effects of disease, disability, or psychological distress on quality of life and outcomes. Beginning in FY 2008, progress toward achieving this goal will be updated annually in the NIH section of the President's budget submission in a report on NIH GPRA responsibilities.

- For more information, see http://officeofbudget.od.nih.gov/ui/HomePage.htm
- (E) (**NINR**, NCI) (GPRA Goal)

Acupuncture for Osteoarthritis of the Knee: Clinical trials supported by NIH and others suggest that acupuncture may have a useful role in treating a variety of chronic painful conditions, hypertension, and obesity. For example, in 2006 NIH-funded investigators reported findings from the longest, largest, randomized, controlled clinical trial of acupuncture ever conducted. The results demonstrated that acupuncture is an effective adjunct to conventional treatment for osteoarthritis, the most common form of arthritis and a major cause of pain, limitation of activity, and health care utilization among the elderly. Study subjects receiving acupuncture had significantly reduced disability and improved quality of life. The innovative trial design resulted from an interdisciplinary collaboration of rheumatologists, licensed acupuncturists, and biostatisticians, ensuring that the research methodology was scientifically sound and accurately reflected acupuncture as traditionally practiced.

- Manheimer E, et al. *Acupunct Med* 2006;24:S7-14, PMID: 17308513
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research.*

Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA): This 5-year clinical study's longitudinal design will greatly accelerate the identification of better treatments to control the pain of temporomandibular muscle and joint disorders. The OPPERA study marks one of the first prospective clinical studies of a chronic pain disorder. A prospective study is the "gold standard" of medical research: it looks forward in time, monitoring the health of those in the study over several years to track the onset or progression of a disease. With the study's 5-year vantage point, investigators will begin identifying individual genetic, physiologic, and psychological factors that cause or contribute to temporomandibular muscle and joint disorders and advance virtually all aspects of understanding and caring for these disorders.

- For more information, see http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/NRY2005/PR12052005.htm
- For more information, see see http://www.nidcr.nih.gov/Research/ResearchResults/InterviewsOHR/TIS012006.htm
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIDCR)

Spine Patient Outcomes Research Trial (SPORT): Before SPORT, many patients with back pain were conflicted about whether to undergo surgery. Now, people who have back pain due to a herniated disc can be assured that a surgical procedure called lumbar diskectomy is generally effective in relieving pain from herniated discs, but, if their pain is tolerable, their symptoms will probably subside, even without surgery, over time. On the other hand, if a patient has spondylolisthesis with stenosis, they are likely to benefit more from decompression and fusion surgery than from nonoperative treatments.

- Weinstein JN, et al. *JAMA* 2006;296:2441-50, PMID: 17119140
- Weinstein JN, et al. *JAMA* 2006;296:2451-9, PMID: 17119141
- Weinstein JN, et al. *N Engl J Med* 2007;356:2257-70, PMID: 17538085
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/backpain_surgery.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/06_28.asp
- This example also appears in Chapter 3: *Clinical and Translational Research.*

- (E) (**NIAMS**, NIOSH, ORWH)

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

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*

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*
- *Long-Range Research Plan for Digestive Diseases (expected to be completed in 2008)*

National Institute of Allergy and Infectious Diseases (NIAID)

- *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis (2001)*
- *Vaccine Research Center Strategic Plan: Research Toward Development of an Effective AIDS Vaccine (2001)*
- *NIAID Plan for Research on Immune Tolerance (1998)*

National Eye Institute (NEI)

- *NIH Action Plan for Transplantation Research (2007)*
- *National Plan for Eye and Vision Research (2004)*

- *Vision Research—A National Plan 1999-2003: A Report of the National Eye Advisory Council*
- *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*

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*

National Institute of Mental Health (NIMH)

- *NIMH Strategic Plans and Priorities*
- *Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research*
- *Pathways to Health: Charting the Science of Brain, Mind, and Behavior*

National Institute on Drug Abuse (NIDA)

- NIDA Draft Strategic Plan

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*

National Institute of Nursing Research (NINR)

- *NINR Strategic Plan: Changing Practice, Changing Lives*

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 (Draft)*

Office of AIDS Research (OAR)

- *FY 2008 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)
- *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)
- *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)

Detailed Burden of Illness and Related Health Statistics

The following summary illustrates the depth and breadth of chronic disease burden (all statistics refer to the U.S. population unless otherwise specified):

Cardiovascular Diseases [63]	*Coronary heart disease* Mortality: 452,000 (2004) Prevalence: 15.8 million (2004) *Heart failure* Mortality: 58,000 (2004) Prevalence: 5.2 million (2004) *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[64]	*Chronic obstructive pulmonary disease* Mortality: 120,000 (2004) Prevalence: 12 million people diagnosed; additional 12 million undiagnosed (2004) *Asthma* Mortality: 4,000 (2004) Prevalence: 22 million (2004) Total costs (direct and indirect): $12.7 billion (1998) *Cystic Fibrosis* Prevalence: 30,000 Incidence: 1 in every 3,000 newborns
Diabetes Mellitus [65]	Mortality: 224,092 (2002); 6th leading cause of deathe Prevalence: 20.8 million (diagnosed and undiagnosed); type 1 diabetes accounts for 5-10% of diagnosed cases (2005) Total costs (direct and indirect): $132 billion (2002)

Obesity[66]	Prevalence: 34.1 percent of adults are overweight; 32.2% adults are obese; 18.8% children (aged 6-11) and 17.4% adolescents (aged 12-19) are overweight (2004) Total health care costs (direct and indirect): $117 billion (2000)
Chronic Kidney Disease[67]	Prevalence: 3.83% adults (7.7 million people) (1999-2000) Costs: $32.5 billion for treating end-stage renal disease (ESRD) (2004)
Urologic Diseases[68]	*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: 34% of adults (62.7 million) self-reported at least one occurrence (1988-1994) Cost (direct): $3.5 billion (2000)
Digestive Diseases[69]	Mortality: 234,000 (2002) Prevalence: 60-70 million people (1996) Disability: 1.9 million people unable to perform daily activities (1990-1992) Costs: $85.5 billion (direct); $20 billion (indirect) (1998)
Chronic Liver Disease [70]	*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 billion (1998) *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[71]	*Sickle cell disease* Prevalence: 70,000; 1 in 500 African American births; 1 in 1,000-1,400 Hispanic-American births *Thalassemia* (includes Cooley's anemia) Prevalence: 1,000 *Hemophilia* Prevalence: 18,000 Incidence: 400 newborns each year
Musculoskeletal Diseases[72]	*Osteoarthritis* Prevalence: 12.1% of adults (21 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[73]	Prevalence: At any given time, 1 in 3 people has a skin disease. Total health care costs: >$34.3 billion (2003) *Atopic dermatitis* Prevalence: >15 million Costs (to health insurance companies): >$1 billion
Eye Diseases[74]	*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[75]	*Hearing loss* Prevalence: 2-3 of 1,000 newborns; 15% (32.5 million) adults; 10% (22 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[76]	*TMJ disorder* Prevalence: 5-12% of the population; twice as prevalent in women as men *Chronic periodontitis* Prevalence: 80% of adults with 1 in 5 having severe periodontitis *Mental disorders* Prevalence: 6% of adults (approximately 12.5 million) have a serious
Mental Illness[77]	*Mental disorder* Disability: No. 1 leading cause; accounts for 29.6% of all disability adjusted life years (DALYs) (U.S. and Canada) Cost: $63 billion lost to decreased productivity *Depression* Prevalence: 2% of adults (approximately 4.4 million) have a serious depressive disorder Disability: leading cause among mental health disorders; accounts for 11.2% of all DALYs (U.S. and Canada) Cost: $36.2 billion due to lost work; $51.5 billion including lost productivity while at work
Alcohol Use Disorders[78]	*Alcohol use disorders* Prevalence: 18 million (8.5% of the population aged 18 or older) *Alcohol-attributable chronic disease* Total costs: $122 billion (est.) Disability: Alcohol use is the 7th leading cause of DALYs
Addiction[79]	Total cost: >$500 billion (est.; includes health- and crime-related costs as well as losses in productivity)-approximately $181 billion for illicit drugs, $168 billion for tobacco, and $185 billion for alcohol. *Abuse or dependence on alcohol and illicit drugs* Prevalence: 22.2 million people or 9.1% of the population aged 12 or older (est.) (2005) *Cigarette smoking* Mortality: 440,000 (2002)

[56] A composite.
[57] Hedley AA, et al. *JAMA* 2004;291:2847-2850, PMID: 15199035
[58] Quam L, et al. *Lancet* 2006;368:1221-3, PMID: 17027712

[59] For more information, see: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/leadingdeaths03/leadingdeaths03.htm
[60] For more information, see: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/leadingdeaths03/leadingdeaths03.htm
[61]For more information, see: http://heal.niehs.nih.gov/about.htm
http://www3.niaid.nih.gov/research/topics/allergies/default.htm
[62] For more information, see http://www.nih.gov/about/researchresultsforthepublic/AlcoholDependenceAlcoholism.pdf; http://www.nih.gov/about/researchresultsforthepublic/DrugAbuseandAddiction.pdf; http://www.nih.gov/about/researchresultsforthepublic/Tobaccoaddiction.pdf;
[63]For more information, see http://www.nhlbi.nih.gov/about/factbook/toc.htm (chapter 4. Disease Statistics); http://www.nhlbi.nih.gov/health/dci/index.html
[64]For more information, see http://www.nhlbi.nih.gov/about/factbook/toc.htm (chapter 4. Disease Statistics); http://www.nhlbi.nih.gov/health/dci/index.html; Weiss KB. *J Allergy Clin Immunol* 2001;107:3-8, PMID: 11149982
[65]For more information, see http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf
[66]For more information, see http://win.niddk.nih.gov/statistics/index.htm; Ogden CL et al. JAMA 2006;295:1549-55, PMID: 16595758
[67]For more information, see http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/index.htm
[68]For more information, see http://kidney.niddk.nih.gov/statistics/uda/index.htm; http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/index.htm
[69]For more information, see http://digestive.niddk.nih.gov/statistics/statistics.htm
[70]http://www.cdc.gov/nchs/data/nvsr/nvsr55/nvsr55_19.pdf; http://www.cdc.gov/ncidod/diseases/hepatitis/resource/dz_burden.htm; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5337a2.htm; *National Vital Statistics Report* 2007;55:1-119, PMID: 17867520;
Sandler RS, et al. *Gastroenterology* 2002;122:1500-1511, PMID: 11984534
[71]http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5337a2.htm; http://www.cdc.gov/ncbddd/hbd/thalassemia.htm
[72]http://www.niams.nih.gov/Health_Info/Osteoarthritis/default.asp;
[73]For more information, see http://www.niams.nih.gov/Health_Info/Atopic_Dermatitis/default.asp
[74]For more information, see Friedman DS, et al. *Arch Ophthalmol* 2004;122:564-72, PMID: 15078675; Gritz DC, Wong IG. *Ophthalmol* 2004;111:491-500, PMID: 15019324; Nussenblatt RB. Int *Ophthalmol* 1990;14:303-8, PMID: 2249907; Kempen JH et al. *Ophthalmol* 2004;122:552-63, PMID: 15078674; Friedman DS, et al. *Arch Ophthalmol* 2004;122:532-8, PMID: 15078671
[75]For more information, see http://www.nidcd.nih.gov/health/hearing; http://www.nidcd.nih.gov/health/balance;
[76]For more information on TMJ disorder, see see http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/FacialPain/; for more information on chronic periodontitis, see http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/GumDisease
[77]For more information, see http://www.who.int/whr/2004/annex/topic/en/annex_3_en.pdf; http://www.mentalhealthcommission.gov/reports/FinalReport/toc.html; Kessler RC, et al. *Arch Gen Psych* 2005;62:617-27PMID: 15939839; Greenberg PE, et al. *J Clin Psychiatry* 2003;64:1465-75 PMID: 14728109
[78]For more information, see http://pubs.niaaa.nih.gov/publications/economic-2000/alcoholcost.PDF; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5337a2.htm; Grant BF, et al. *Arch Gen Psychiatry* 2004;61:807-16, PMID: 15289279; Michaud et al. *Population Health Metrics* 2006;4:11, PMID: 17049081
[79]For more information, see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5337a2.htm; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5425a1.htm; Office of National Drug Policy. The Economic Costs of Drug Abuse in the United States: 1992-2002. Washington, DC: Executive Office of the President (Publication No. 207303); http://www.oas.samhsa.gov/NSDUH/2k5NSDUH/2k5results.htm; http://www.cdc.gov/MMWR/preview/mmwrhtml/mm5114a2.htm;

Summary of Research Activities by Disease Categories

Life Stages, Human Development, and Rehabilitation

In 1961, Dr. Robert Guthrie, a pediatrician and microbiologist, developed a simple test, using a "heel-stick" drop of blood, to detect phenylketonuria (PKU) in newborn infants. This rare, inherited disease interferes with the body's capacity to metabolize protein. Unless treated almost immediately with a special diet, PKU progressively derails a child's intellectual development. Children with untreated PKU may appear healthy as newborns, but by age 3 to 6 months, they begin to lose interest in their surroundings, and by 1 year of age, their intellectual function is irreversibly impaired. Dr. Guthrie's discovery has allowed for rapid, inexpensive screening of all infants at birth. Those identified with PKU can be started on the preventive diet and escape the disorder's permanent damaging effects. Building on Dr. Guthrie's discovery, NIH-supported scientists developed an additional newborn screening test, this time for congenital hypothyroidism. Like PKU, this condition may not be apparent at birth, but unless simple preventive treatment begins almost immediately in affected infants, irreversible damage to the developing brain occurs within months. All states now mandate newborn PKU and hypothyroidism screening, and the developmental disability associated with these two disorders has all but disappeared in the United States.

Introduction

From before conception through old age, complex biological processes interacting with physical and psychosocial factors in an environment determine health and functioning at any given life stage and provide the foundation of the next stage. NIH research in this area encompasses the formation and development of cells, tissues, organs and organ systems, as well as the physical, cognitive, and behavioral characteristics of the child, adolescent, and adult in his or her environment. Although developmental processes proceed most rapidly in gestation and the early years of childhood, they continue throughout the course of life.

This area of research includes studies of normative processes of growth, maturation, and aging. Understanding "what goes right" developmentally at each life stage is critical to discovering how to protect and enhance human health and functioning. Knowledge from such normative research also is essential to understanding the role of developmental vulnerabilities in the origins, expression, prevention, and treatment of illness and injury. For example, understanding the normal brain immaturity of adolescents is essential to understanding aberrant behaviors of youth and developing interventions that will work for them. Similarly, understanding normal, progressive maturation and functional decline in relation to disease processes is key to discovering better interventions to extend healthy active years of life. At all life stages, normative data on physical and psychosocial development are critical to designing effective rehabilitative interventions.

Individuals may experience underdeveloped, lost, damaged, or deteriorated function during any of the life stages. Medical rehabilitation research is the study of physiologic mechanisms, methods of treatment, and devices that serve to improve, restore, or replace these functions. This research includes translating new knowledge into medical, behavioral, psychological, social, and technological interventions to optimize impaired functioning. A key aspect of medical rehabilitation research is its focus on the effects of functional impairment on the whole person, rather than on a single organ system. Thus, it views the person in the context of a system of interacting variables, including psychosocial, organic, and environmental.

By necessity, the scope of NIH research on life stages, human development, and rehabilitation is broad. Dynamic, ongoing interactions among developmental processes and physical and psychosocial environmental factors are implicated in a wide range of disorders and disabilities. Research in this area includes basic, clinical, epidemiological, and translational studies of normative processes and of many chronic diseases such as cancer, obesity, osteoporosis, and cardiovascular and metabolic disorders. Also included is research on mental illness, addiction, and cognitive disabilities such as intellectual disability, autism, and Alzheimer's disease. Whereas the section "Chronic Diseases and Organ Systems" in this report addresses these conditions generally, this section focuses on life stage and developmental dimensions of chronic and other conditions and on rehabilitative interventions.

NIH Institutes dedicated to specific disorders and organ systems incorporate life stages and developmental perspectives into their research initiatives and projects. For example, NCI supports research on how cancer risk and therapies may differ in children, adults, and the elderly. Among NIDCR's research priorities are studies of genetic and environmental interactions that may explain disfiguring birth defects of the head, face, and mouth. NINR and NIAAA strategic plans incorporate a life-course approach.

As the Institute with statutory responsibility for child health and human development research, NICHD conducts and supports research programs in reproductive health and the developmental processes that begin before conception and continue through gestation, birth, infancy, childhood, and adolescence. As the Institute charged with research on aging, NIA conducts and supports research on both the maintenance and loss of functions during the aging process, diseases associated with aging, and the problems and needs of older individuals and their caregivers. NINR conducts research focused on establishing a scientific basis for patient care across all life stages and is designated the lead NIH Institute for end-of-life research. NIEHS focuses on the influences of environmental agents on the development and progression of human disease.

Mission-specific rehabilitation research is supported by 18 Institutes, including NIA, NIBIB, NICHD, NIDCR, and NINDS. A focal point for this area is the National Center on Medical Rehabilitation Research, within NICHD, which emphasizes the rehabilitation and lifelong care of people with physical disabilities resulting from injury, stroke, and other disorders.

Burden of Illness and Related Health Statistics

Because of the wide range of disorders studied in NIH life stages, human development, and rehabilitation research, data on the health and economic costs of specific conditions are presented throughout this report. This section presents selected examples of general data on lifetime burdens of illness and on burdens at the beginning and later stages of life.

Lifetime Burden

From birth to death, per-person health care costs in the United States have been estimated to average $316,579 in 2000 dollars. Of this total, an estimated 7.8 percent of health care costs accrue from birth to age 20, 12.5 percent between ages 20 and 39, 31.0 percent between ages 40 and 64, and 48.6 percent, or almost half of all lifetime health care expenditures, after age 65[80]. Between 1992 and 1996, 22 percent of all medical expenditures for the

[80] Alemayehu B, Warner KE. *Health Serv Res* 2004;39:627-42, PMID: 15149482

period after age 65 occurred in the last year of life[81]. Although rates of self-reported disability in people age 65 and older have been declining in recent years, any cost savings from this trend may be offset by the burgeoning growth of this population as a proportion of U.S. residents[82]. Between 2000 and 2050, the proportion of this older population is expected to increase from 5.9 percent to 11.6 percent of U.S. residents.

Early Origins of Disease and Disability

Preterm birth and the associated problem of low birth weight signal the potential for significant developmental problems that may originate in the prenatal period, or even before, as a result of a family's genetic makeup and its environmental exposures[83]. Preliminary data indicate that in 2004-2005, 12.7 percent of U.S. births were preterm, a rate that has risen 20 percent since 1990. Infants born with low birth weight in 2005 comprised 8.2 percent of births, an increase of more than 20 percent since the mid-1980s[84].

Although medical advances and supportive environments enable increasing numbers of preterm infants to survive and to "catch up" developmentally in childhood, the health and economic burdens associated with these births begin immediately and may last a lifetime. In 2001, costs for preterm, low-birth-weight hospital admissions were $5.8 billion in the United States, or 47 percent of the costs of all hospital stays of infants[85]. Preterm birth accounts for one of five children with intellectual disability, one of three children with vision impairment, and almost half of children with cerebral palsy. For an individual with intellectual disability, lifetime costs of medical care, special education, residential care, lost wages, and other associated expenditures are estimated to be $1,014,000 in 2003 dollars[86].

Later Emergence of Disease and Disability

Aging comprises a set of dynamic biological, physiological, and psychosocial processes and systems that are interactive and independent and that result in wide variations in health outcomes and functioning. For some individuals, sensory, cognitive, and physical capacities continue at remarkably high levels for decades. For others, increasing age is accompanied by a significant, progressive decline in almost all physiological functions and a significantly increased risk of age-related chronic diseases and disability. Recent estimates indicate that approximately 80 percent of all individuals in the United States who are 65 years or older have at least one chronic condition, and 50 percent have at least two[87].

The marked variability among older adults in aging processes and disease burden may be explained in part by risks incurred in earlier decades. For example, periods of rapid tissue growth in gestation, early childhood, adolescence,

---

[81] Hoover DR et al. *Health Serv Res* 2002;37:1625-42, PMID: 12546289

[82] Freedman VA et al. *JAMA* 2002;288:3137-46, PMID: 12495394

[83] Drake, AJ, Walker BR. *J Endocrinol* 2004;180:1-16, PMID: 14709139

[84] For more information, see http://www.cdc.gov/nchs/products/pubs/pubd/hestats/prelimbirths05/prelimbirths05.htm

[85] Russell RB, et al.*Pediatrics* 2007;120:e1-e9, PMID: 17606536

[86] For more information, see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5303a4.htm

[87] For more information, see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5206a2.htm

and during pregnancy may be periods of heightened risk to later-emerging cancers[88]. Low birth weight is related to increased risk in adults for cardiovascular disease, such as myocardial infarction, stroke, and hypertension[89]. Maternal diabetes during pregnancy may increase the risk of diabetes and obesity in offspring[90]. Prenatal influences also may increase risks of osteoporosis[91] and Alzheimer's disease[92]. In each case, discovering effective interventions at early stages in life could contribute to lower burdens of disease and disability associated with aging.

NIH Funding for Life Stages, Human Development, and Rehabilitation Research

In FYs 2006 and 2007, NIH funding for rehabilitation research was $324 million and $344 million respectively. Currently, NIH does not collect trans-NIH funding data on the category of life stages and human development research. The table at the end of this chapter indicates some of the research areas involved in this investment (see "Estimates of Funding for Various Diseases, Conditions, and Research Areas").

Summary of NIH Activities

The goal of life stages, human development, and rehabilitation research is to enable people to achieve a full lifespan with the best health and function at every life stage. Understanding complex developmental pathways to health or illness throughout life is critical to creating new ways to prevent disease and disability before they become symptomatic—or even preempting the disease process before it starts. Developmental stages also are an important consideration in rehabilitation research. For example, differences between age groups such as physical size, physiological processes, psychosocial trajectories, and expected lifespan must be taken into account in planning rehabilitation for an individual. A central goal of research is to provide the scientific evidence needed to support developmentally appropriate rehabilitation plans.

The fundamental concepts of developmental science, such as "developmental windows," can be brought to bear whether a research project focuses primarily on normative development, multiple life stages, a specific life stage, or rehabilitation. These "windows" are periods in the life of a cell, a fetus, a child, or an adult when the normal processes of growth and maturation may be more sensitive to the effects of external factors, often referred to as "environmental influences." Because human development progresses in a multifaceted environment, scientists study a wide range of external factors that could have adverse or protective effects on human health and functioning. This research might examine the effects of physical agents such as, for example, diet, exercise, pesticides, industrial chemicals, or mold. But it also might investigate the influences on health and development of factors such as parenting styles, family structure, education, community social norms and economic status, and/or intergenerational influences.

---

[88] [88]Potischman N, et al. The life course approach to cancer epidemiology. In: *A Life Course Approach to Chronic Disease Epidemiology.* Second Edition. Kuh D, Ben-Shlomo Y (eds). Oxford University Press, New York, 2004, p. 260-80.

[89] Rich-Edwards JW, et al. *BMJ* 1997;315:396-400

[90] Dabelea D, Pettitt DJ. *J Pediatr Endocrinol Metab* 2001;14:1085-91, PMID: 11592564

[91] Javaid MK, Cooper C. *Best Pract Res Clin Endocrinol Metab* 2002;16:349-67, PMID: 12064897

[92] Basha MR et al. *J Neurosci* 2005;25:823-9, PMID: 15673661

Normative Research

Scientists' efforts to identify and understand interactions among developmental processes and external factors are being accelerated by powerful new technologies. For example, advanced imaging technologies are being used to create a robust database of normal brain development during childhood and adolescence. The resulting data will enable scientists to better understand the atypical developmental processes associated with autism, intellectual disability, and other developmental disorders. Novel analytic techniques developed in genomics research have created new research opportunities in the emerging field of epigenetics. This new field builds on discoveries that the timing of gene functions—the "on" and "off" switches that control myriad biological processes—can be altered without changing the structural DNA "coding" of a gene. The health effects of these subtle and potentially reversible alterations may be transient or may persist and even be passed down from parent to child. One new NIH initiative in developmental epigenetics focuses on alterations in gene expression that may occur spontaneously or in response to environmental exposures well before birth. Multiple initiatives, comprising a Roadmap Epigenomics Initiative, are intended to develop comprehensive reference maps of the epigenome and to develop new analytic technologies.

In other normative research, a long-term study of women before, during, and after menopause is designed to improve understanding of the health effects, psychosocial influences, and subsequent health consequences of this major life stage for women. Extended studies of older populations are enabling scientists to disentangle the effects of disease from the normal aging process.

Discoveries by NIH-supported scientists conducting normative research have enabled them to preempt the development of cleft palates in experimental mice that were bred to manifest this disabling defect. Having identified a protein that influences the development of certain undifferentiated cells in the embryo, scientists then identified the critical point in normal embryonic development of the palate, or roof of the mouth. They subsequently manipulated the protein at that point in development to reverse the initiation of the clefting process in the mice.

Multistage Research

NIH research encompassing multiple developmental or life stages seeks to understand what factors early in life may contribute to health or to health risks in later life (see also the section "Epidemiological and Longitudinal Studies" in Chapter 3). This conceptual model builds on seminal "life course" studies that found clues to the origins of adult chronic diseases in the earliest period of human life-gestation. The first life course studies linked the risk of heart disease, stroke, hypertension, and diabetes in adults to adaptation of the fetus to inadequate nutrient supply in utero[93].

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 wider array of potentially influential environmental factors. For example, the National Children's Study (NCS) is designed to enroll women who intend to become pregnant and to follow their pregnancies and then their children from birth to age 21. Investigators will use multiple techniques to examine many aspects of the children's lives over time—from family genetics, to the constructed environment of neighborhoods and schools, to chemical exposures linked to the atmosphere, food, and water supplies. The overall NCS goal is to understand the relationships among multiple exposures and multiple health outcomes. NIH also is

[93] Barker DJP. *Clin Sci* (Lond)1998;95:115-28, , PMID: 9680492

collaborating with the Norwegian National Public Health Institute in a long-term prospective cohort study of pregnant women and their children, in which a variety of exposure and health variables will be investigated.

Other studies encompassing more than one life or developmental stage investigate specific factors and/or specific health outcomes. For example, investigators within a consortium of NIH-supported research centers study a range of prenatal to adult environmental exposures that may predispose a woman to breast cancer. NIH-supported scientists use longitudinal studies, imaging and genetics tools, and animal studies to examine the contribution of in utero drug exposure to emotional and cognitive development and to vulnerability to later substance abuse and other mental disorders. Research on the long-term safety of fetal and infant exposure to anti-HIV (antiretroviral) drugs, administered to prevent HIV transmission from an infected woman to her child, is one of numerous NIH research efforts in HIV/AIDS. Cohorts of long-term cancer survivors, including those treated in childhood and at other life stages, are being followed to identify the health and developmental effects of cancer drugs and radiation treatments. Known adverse effects include damage to heart muscles; neurocognitive problems; reproductive health problems, including infertility; pain; and second malignancies, as well as anxiety and depression, discrimination in employment and insurance, and general quality of life. This “survivorship” research ultimately seeks to optimize physiological, psychosocial, and functional outcomes for cancer survivors and their families.

Stage-Specific Research

NIH research that focuses on a single life stage seeks to understand the developmental vulnerabilities of that stage and their implications for risk of disease or disability and for effective interventions. For example, sensitivity of the rapidly developing fetus and the newborn to a variety of inborn and external risk factors is the subject of extensive NIH-supported research efforts. Included in this research are ongoing research programs on stillbirth, preterm birth, SIDS, fetal alcohol syndrome, and birth defects. In one study, scientists found that preterm infants could go home earlier from neonatal intensive care units if their parents received an educational and behavioral intervention that began shortly after their child's admission to the unit and continued after the child went home. During the intervention, fathers as well as mothers learned about the appearance and characteristics of preterm infants and how best to parent their child. This research also found that the intervention lessened mothers' anxiety, depression, and overall parenting stress and increased fathers' involvement in infant care.

School-age children are an important research population because habits that can protect an individual's health, or increase his or her risk of later disease or disability, may be established in this developmental period. Examples of this research include testing a middle-school intervention to lower the risk of developing type 2 diabetes in children as they approach adolescence. Once considered an “adult” disease, type 2 diabetes increasingly is seen in children as rates of pediatric obesity continue to rise. To investigate the potential of the school environment to promote the adoption of long-term healthy behaviors, the experimental program is testing the effects of offering healthier food choices in school cafeterias and vending machines, lengthening and intensifying periods of physical activity, and deploying communication campaigns. In another example, scientists have developed a large body of evidence about how children learn to read and are now investigating differences in how children learn math and science. Research into learning processes for children both with and without learning disabilities permits the development of evidence-based teaching methods so that children with a range of abilities can learn these critical subjects. Major developmental disabilities in children, including intellectual disability and autism, also are the subject of ongoing research.

Adolescence, the developmental period in which the immature brain and teenage social contexts may explain risk-taking behaviors, is another focal point of life stages and human development research. Carefully designed studies on teen and college-age substance-abusing behaviors and teen driving are providing the scientific basis for new

interventions. Studies of the unique challenges in clinical management of youth with HIV or at risk of infection, and of pharmacological therapies for young people with depression and suicide risk, are yielding important guidance for clinicians. Models for delivering needed services to youth with mental illness as they transition to adulthood are being tested.

Another significant area of stage-specific research encompasses the period in which couples start families. Reproductive health research includes expanding fundamental knowledge of processes that underlie human reproduction, investigating ways to alleviate human infertility, and developing and testing new contraceptive options for men and women. Basic, clinical, and translational studies aim to increase understanding of normal reproduction and reproductive pathophysiology and to develop more effective strategies for diagnosing, treating, and preventing conditions that compromise reproductive health. To advance research in this area, the NIH sponsors training programs for reproductive health researchers, including obstetricians and gynecologists.

As individuals age, interactions among normal aging processes and risks acquired early in life and/or cumulatively over the course of life may heighten their vulnerability to disease and disability. For example, many conditions that emerge or worsen in aging individuals are characterized by inflammation, which leads over time to changes in cell tissue and organ structure and function. These changes may contribute to frailty, independent of overt disease, and also may increase susceptibility to, and rate of progression in, chronic diseases. NIH-supported projects include studies of vascular inflammation and neurotoxicity in the aging brain and inflammatory response to loss of sleep. The breadth of NIH research in aging processes is illustrated by an initiative on the psychological mechanisms that guide economic decisions of older people and the underlying neurobiological pathways of their economic behaviors. End-of-life studies focusing on enhancing communications among individuals, families, and clinicians and on measuring care outcomes are intended to enable those involved to better manage this experience. An NIH state-of-the-science conference on end-of-life care and publication of conference proceedings were designed to survey and assess recent advances and to chart additional new directions for this area of research.

Rehabilitation Research

Rehabilitative interventions to enable individuals to gain or recover functions lost to illness or injury may be needed at any life stage. Research in this area recognizes the need for specialized approaches for infants and children at the beginning of the developmental span, for mature adults, and for older people experiencing cumulative effects of normal aging processes and chronic disease. For example, the decline in disability among older people raises questions of whether and how this trend can be maintained or even accelerated. Enabling older people to maintain their health and independence for as long as possible is a major goal of NIH-supported rehabilitation research. Among efforts to reach that goal are projects that are developing and testing exercise and motor-learning interventions for adults who have experienced stroke, hip fracture, and other chronic debilitating diseases and conditions. An important priority in this research is translating findings from the clinical research setting into effective and accessible rehabilitative programs based in communities.

In other rehabilitation research, NIH-supported scientists are applying the newest technology to hasten recovery from and lessen disabling effects of disease and injury. Multiple research projects are focused on novel technologies to supplement or restore lost nervous system functions. Examples include studies to develop devices designed to restore the capacity of people with spinal cord injuries to stand and to control bowel and bladder function. Scientists also are investigating technologies to control seizures as well as brain-machine interfaces to allow persons with paralysis to control devices directly with their brains. To improve rehabilitation for upper-limb paralysis, NIH is supporting the development of robotic exoskeletons that could ultimately provide therapies for

stroke patients in their homes and elsewhere. To expand the mobility of soldiers and others who have lost limbs to injury, NIH-funded research includes studies of a new "intelligent" artificial knee joint. Investigators also are developing ways to implant an artificial limb directly onto the bone of a residual limb, eliminating the need for irritation- and infection-prone socket devices. Even more technologically advanced options for replacing irretrievably injured body parts may one day result from pioneering research in tissue regeneration.

Notable Examples of NIH Activity

Key for Bulleted Items:

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., (policy, planning, and communication)
COE = Supported through a congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = Concerns progress tracked under the **G**overnment **P**erformance and **R**esults **A**ct

Normative Research

Developmental Epigenetics: This rapidly evolving area of research examines how nonstructural changes in gene expression during normal developmental processes can influence health outcomes across the generations. NIH is expanding its research in this area to help scientists learn how typical epigenetic changes and variations occur at the molecular level, starting well before birth. Understanding these epigenetic changes—how they are inherited and passed on to subsequent generations and what factors influence them—could hold the scientific key to understanding and modifying certain factors that lead to a number of diseases or conditions, from obesity to heart disease.

- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (I) (NICHD)

Researchers Report Chemical Rescue of Cleft Palate in Mice: A growing understanding of the multiple roles played by the enzyme GSK3 has enabled scientists to realize that this protein molecule has a role in determining the developmental fates of certain undifferentiated cells in the embryo. A few years ago, this realization led a team of scientists to develop a technique that prompts small molecules directly to turn GSK3 on and/or off with a high degree of precision at different stages of fetal development. In the March 1 issue of the journal Nature, NIH-supported scientists and their colleagues reported using this on-off technique to determine the critical developmental period of the palate, or roof of the mouth, in mice. Remarkably, the researchers showed that, by turning GSK3 back on in pregnant mice during this key developmental window, their embryos in most cases corrected their developing cleft palates. As they reported, five out of nine mouse pups had complete reversal of the developing cleft, and another newborn had a partial rescue of the cleft. As the authors noted, "New approaches to rescuing selected developmental defects require detailed knowledge of timing and levels of protein expression; our studies provide an improved method for defining these experimental conditions in vivo."

- Liu KJ, et al. *Nature* 2007;446:79-82, PMID: 17293880
- This example also appears in Chapter 3: *Molecular Biology and Basic Science.*

- (E)(NIDCR)

MRI 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, as well as 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. The data will be disseminated as a Web-based, user-friendly resource to the scientific community.

- Evans AC, et al. *Neuroimage* 2006;30:184-202,PMID: 16376577
- 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**, NINDS, NIDA, NIMH)

Study of Normal Brain Development: The NIH Intramural Research Program is conducting studies to explore brain development with MRI in healthy children and adolescents. Recent studies have addressed differences in brain structure related to risk for Alzheimer's disease and sex differences in brain development trajectories.

- Shaw P, et al. *Lancet Neurol* 2007;6:494-500, PMID: 17509484
- Lenroot RK, et al. *Neuroimage* 2007;36:1065-73, PMID: 17513132
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NIMH)

National Longitudinal Study of Adolescent Health (Add Health): Several NIH Institutes are supporting this study, which integrates biomedical, behavioral, and social science data to discover the pathways that lead to health and/or disease in adulthood. The NIH initially funded Add Health in 1994 as a social science study of the causes of adolescent health problems and health-related behaviors. As the cohort of adolescents has moved into early adulthood, the study's focus has shifted to the environmental, behavioral, and biological pathways that lead to the development of adult chronic disease. The study initially incorporated measurements of social environments—peer groups, families, schools, and neighborhoods—that could affect health and also incorporated a sibling-pair design that facilitated quantitative genetic studies. Most recently, in collaboration with other Federal offices, NIH funded a new wave of interviews that will include the collection of genetic data and biological markers of disease processes, as well as basic social, individual, and behavioral data. The new design was developed by a collaborative team representing the fields of epidemiology, cardiology, psychology, sociology, behavioral genetics, nutrition, biostatistics, anthropology, medicine, molecular virology, statistics, and survey research.

- For more information, see http://www.cpc.unc.edu/addhealth
- (E) (**NICHD**, NCI, NCMHD, NIA, NIAID, NIDCD, NINR, NIAAA, NIDA, OAR, OBSSR, ORWH)

Study of Women's Health Across the Nation (SWAN): The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in ethnically diverse cohorts. Now in its 14th year, SWAN involves seven clinical field sites supported by a central reproductive hormone laboratory, a coordinating center, an advisory panel, and a repository of blood, urine, and DNA specimens. Used in numerous studies, SWAN data have resulted in important findings. For example, changes in bone density occur from premenopause through late perimenopause; premenopausal women have a significantly lower prevalence of forgetfulness than do women at later menopausal stages; and a high body mass index (BMI) is

not only associated with insulin resistance, which dramatically increases the risk of cardiovascular disease, but also with different menopausal hormonal patterns relative to normal BMI.

- (E) (**NIA**, NINR, NCCAM, NICHD, NIMH, ORWH)

Baltimore Longitudinal Study of Aging (BLSA): In 2008, NIA will celebrate the 50th anniversary of the BLSA, America's longest-running scientific study of human aging. More than 1,400 men and women ranging in age from the 20s to the 90s have been study volunteers. The BLSA has generated significant findings to elucidate the normal course of aging and disentangle the effects of disease from the normal aging process.

- For more information, see http://www.grc.nia.nih.gov/branches/blsa/blsa.htm
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (I) (NIA)

Health and Retirement Study (HRS): The HRS is the leading source of combined data on the health and financial circumstances of Americans over age 50 and is a valuable resource to follow and predict trends and help inform policies for an aging America. Now in its 14th year, the study follows more than 20,000 people at 2-year intervals and provides researchers with an invaluable, growing body of multidisciplinary data on the older Americans' physical and mental health, insurance coverage, finances, family support systems, work status, and retirement planning. Managed under a cooperative agreement between NIH and the University of Michigan, the study was expanded in 2006 to include additional key constructs in cognitive aging. A substudy will provide the first estimates of cognitive impairment and dementia based on nationally representative data and validation of survey measures. HRS staff will also assemble information on sample and questionnaire design, computer-assisted interview programming, interviewer performance, and data dissemination to improve the quality of data collected and provide an incentive for international partners to follow a harmonized design that will maximize the potential for cross-national behavioral and social research on aging.

- For more information, see http://hrsonline.isr.umich.edu
- (E) (NIA)

Life Stages Research

The National Children's Study (NCS): The 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 manmade environment to basic biological, genetic, social, and cultural influences. By studying children through their different phases of growth and development, researchers will be better able to understand the role of these factors in both health and disease. Specifically, 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 NICHD and NIEHS, CDC, and the Environmental Protection Agency.

- For more information, see http://www.nationalchildrensstudy.gov
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
- (I) (**NICHD**, NIEHS)

Environmental Health of Mothers and Babies: the Norwegian Mother and Child Cohort Study: NIH is participating

in the Norwegian Mother and Child Cohort Study, which provides a valuable opportunity to assess the role of environmental exposures in the health of women and their children. The Norwegian Mother and Child Cohort Study, or MoBa, (den norske Mor and barn-undersØkelsen) is an ongoing, long-term, prospective cohort study of 100,000 pregnant Norwegian women and their children. In collaboration with the Norwegian National Public Health Institute (NIPH), NIH is supporting the collection of additional biologic specimens from the pregnant women. These specimens will be used for the measurement of environmental exposures. A variety of exposure and health variables on babies, mothers, and fathers are collected. Records from the cohort study will also be linked to routine national health registries.

- For more information, see http://www.niehs.nih.gov/research/atniehs/labs/epi/studies
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
- (I) (NIEHS)

The Role of Development in Drug Abuse Vulnerability: NIH supports a number of longitudinal studies at various stages of development, following cohorts over extended time frames. Information is gathered on children's cognitive and emotional development, as well as their vulnerability to addiction later in life. These studies have been critical to estimate, for example, the contribution of in utero drug exposure on emotional and cognitive development, vulnerability to substance abuse, and other mental disorders. This knowledge, together with animal studies that provide complementary and validating information while minimizing the confounding factors that are likely to play a role in prenatal effects of drug exposure in humans, will help us to mitigate the deleterious impact of substance abuse on the developing fetus. With regard to later developmental stages, the application of modern brain imaging technologies has generated unprecedented structural and functional views of the dynamic changes occurring in the developing brain (from childhood to early adulthood). The discovery of these changes has been critical to understanding the role of brain development in decision-making processes and responses to stimuli, including early exposure to drugs. Such studies have suggested, for example, that an unbalanced communication between volitional control and emotional circuits may explain some of the impulsive reactions typical of adolescents, who tend to engage in risky behaviors and are at heightened risk for developing addictions. Collectively, these longitudinal studies, using new imaging and genetics tools, promise a greatly enhanced ability to interpret the effects of myriad environmental variables (e.g., quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics) on brain development and behavior.

- For more information, see http://www.drugabuse.gov/NIDA_notes/NNvol19N3/Conference.html
- For more information, see http://www.nida.nih.gov/NIDA_notes/NNvol19N3/DirRepVol19N3.html
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (**NIDA**, NICHD) (GPRA Goal)

Transdisciplinary Tobacco Use Research Centers: 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.

- For more information, see http://dccps.nci.nih.gov/tcrb/tturc
- This example also appears in Chapter 2: *Cancer.*
- (E) (**NCI**, NIDA, NIAAA)

The Centers for Transdisciplinary Research on Energetics and Cancer (TREC): These centers foster collaboration among transdisciplinary teams of scientists to accelerate progress toward reducing cancer incidence, morbidity, and mortality associated with obesity, low physical activity, and poor diet. The biology and genetics of the many factors that influence diet, physical activity, and obesity across the stages of life are applied to behavioral, sociocultural, and environmental factors, and transdisciplinary training opportunities are provided for scientists. The TREC initiative is interfacing with a number of established NCI initiatives in the area of diet, physical activity, and weight and is integrated with the NIH Obesity Research Task Force Strategic Plan.

- For more information, see http://cancercontrol.cancer.gov/trec
- (E) (NCI)

HIV/AIDS Epidemiological and Long-Term Cohort Studies, Cohorts, and Networks: NIH supports epidemiological HIV research through a wide range of studies, cohorts, and networks that contributes to our understanding of risk factors that lead to HIV transmission and disease progression. Established in 2005, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) compiles data from NIH-funded international HIV research to answer population-level questions about HIV variants and resistance, HIV pathogenesis in different settings, success of antiretroviral therapy, treatment history of HIV in different populations, success of prevention strategies, and vaccines. The Pediatric HIV/AIDS Cohort Study (PHACS) network, established in 2005, addresses two critical pediatric HIV research questions: (1) the long-term safety of fetal and infant exposure to prophylactic antiretroviral chemotherapy and (2) the effects of perinatally acquired HIV infection in adolescents. The Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) are the two largest observational studies of HIV/AIDS in women and homosexual or bisexual men, respectively, in the United States. These studies exceed the scope of clinical care diagnostics and laboratory analysis on both HIV-infected and, importantly, HIV-negative controls, which allows for novel research on HIV spread, how the disease progresses, and how it can best be treated. The groups focus on contemporary questions such as the interactions among HIV infection, aging, and long-term treatment; cardiovascular disease; and host genetics and its influence on susceptibility to infection, disease progression, and response to therapy.

- 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**, NICHD)

Childhood Cancer Survivors Study (CCSS): Although survival rates from childhood cancers are encouraging, researchers have found that these young survivors may particularly suffer from the late effects of treatment. In 2006, CCSS researchers documented serious long-term health issues in adults after radiation for childhood cancers. These findings will change treatment regimen guidelines for current childhood cancers and also have implications for individuals from the study who are now adults. The Children's Oncology Group (COG) has prepared a resource for physicians, “Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.”

- For more information, see http://www.cancer.gov/cancertopics/coping/childhood-cancer-survivor-study
- For more information, see http://www.survivorshipguidelines.org
- This example also appears in Chapter 2: *Cancer.*
- (E) (NCI)

Long-Term Cancer Survivors Research Initiatives: The population of cancer patients surviving more than 5 years continues to grow across life stages, from children through senior adults. These research initiatives focus on the physiological and psychosocial effects of treatment and medical 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. Implications include the length and quality of survival and the ongoing burden of illness and costs.

- For more information, see http://cancercontrol.cancer.gov/bb/2006_bb.pdf#page=93
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-04-003.html
- This example also appears in Chapter 2: *Cancer.*
- (E) (**NCI**, NIA, CDC)

Developmental Windows of Vulnerability to Environmental Exposures: The Breast Cancer and Environment Research Centers supported by NIH function as a consortium to study the impact of prenatal to adult environmental exposures that may predispose a woman to breast cancer. The centers bring together basic scientists, epidemiologists, research translational units, and community advocates within and across the centers to investigate mammary gland development in animals and young girls to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. The overall goals of the BCERC are 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. These public health messages will be based on the integration of basic biological, toxicological, and epidemiological data.

- For more information, see http://www.bcerc.org
- This example also appears in Chapter 2: *Cancer.*
- (E) (**NIEHS**, NCI)

Population Research: Given the Nation's increasing diversity and changing demographics, it is critical to understand how trends in areas such 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.

- The National Longitudinal Survey of Youth (1979 cohort) continues to assess the work, educational, and family experiences of a nationally representative cohort of young men and women who were 14-22 years old when they were first studied in 1979. T he study also follows children born to female participants up through age 20, creating the opportunity to study intergenerational influences on child development, health behaviors, and educational attainment.

  - For more information, see http://www.fragilefamilies.princeton.edu/index.asp
  - For more information, see http://nis.princeton.edu/
  - For more information, see http://www.bls.gov/nls/nlsy79ch.htm
  - This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
  - (E) (**NICHD**, NCI, NCMHD, NIA, NIAAA, NIAID, NIDA, NIDCD, NINR, OAR, OBSSR, ORWH)

Brain Disorders in the Developing World: Research Across the Lifespan: Brain disorders are the leading

contributor to years lived with disability in all regions of the world, with the exception of sub-Saharan Africa. This program boosts research in the developing world on childhood disorders such as cerebral palsy and epilepsy, on mental illnesses such as depression and schizophrenia, and on degenerative disorders such as stroke and Alzheimer's disease. Under this program, U.S. investigators and their foreign collaborators are studying the neurocognitive consequences of HIV/AIDS, the relationship between zinc nutrition and brain development, and the neurological disorders stemming from treatable infectious causes, such as cerebral malaria, cisticercosis, TB, and bacterial sepsis.

- For more information, see http://www.fic.nih.gov/programs/research_grants/brain_disorder
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (**FIC**, NEI, NIA, NIAAA, NICHD, NIDA, NIEHS, NIMH, NINDS, ODS)

Nonalcoholic Steatohepatitis (NASH) Clinical Research Network: NASH is strongly associated with obesity and type 2 diabetes, conditions that have increased dramatically in recent decades. Network research addresses GPRA Goal SRO-4.3. The Network is conducting a randomized clinical trial to evaluate the safety and efficacy of the insulin-sensitizing drug pioglitazone or vitamin E compared with placebo for the treatment of nondiabetic adults with NASH. Also, in a separate trial in children, the network is comparing the insulin-sensitizing drug metformin, vitamin E, and placebo in treating nonalcoholic fatty liver disease.

- For more information, see http://www.jhucct.com/nash
- (E) (**NIDDK**, NICHD, NCI, CRADA with industry) (GPRA)

Acute Liver Failure Study Groups: The adult and pediatric Acute Liver Failure Study Groups address the problem of acute liver failure due to drugs or other factors. The Groups' research has provided knowledge and tools for managing the clinical and public health burden of acute liver failure. In 2002, the adult study group highlighted a dramatic increase in liver injury due to the over-the-counter pain reliever acetaminophen. The groups then developed a serum-based assay to detect acetaminophen-induced acute liver failure in adults and children. Current studies are testing potential therapies to improve survival in patients with acute liver failure.

- Ostapowicz G et al. *Ann Intern Med* 2002;137:947-54 , PMID: 16950959
- For more information, see http://tinyurl.com/2qu94j
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*
- (E) (**NIDDK**, FDA)

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 results in significant increase in lifespan. The CALERIE study will help to determine whether these beneficial effects extend to humans. Results from pilot studies demonstrate that overweight people who cut their calories by 25 percent for 6 months have reduced fasting insulin levels and core body temperature, two markers that may be associated with increased longevity in humans. A long-term study began in January 2007.

- For more information, see http://calerie.dcri.duke.edu
- (E) (NIA)

Stage-Specific Research

Fertility and Infertility: As the CDC has stated, “for many couples who wish to start a family, the dream is not easily realized.” For about 2.1 million married couples who reported not using contraception, the women were still

unable to become pregnant after 1 year. NIH supports research to better understand the basic processes underlying human reproduction and to directly alleviate infertility and reproductive disorders. Much of this effort involves translating rapidly emerging laboratory research into clinical applications. Scientists are working to determine how certain gynecological conditions, such as polycystic ovary syndrome and endometriosis, and certain diseases and disorders of the male reproductive system affect fertility. Some evolving and exciting fertility research is applying cryopreservation technology to the freezing of human eggs to preserve fertility in women undergoing cancer treatment. Scientists are also exploring the link between obesity and fertility and assessing the long-term impact of using assistive reproductive technologies.

- (E) (**NICHD**, ORWH)

Women's Reproductive Health Research Career Development Program: The ORWH cosponsored with NICHD the funding of 20 institutional career development awards designed to increase the number of obstetricians and gynecologists conducting research in women's health.

- For more information, see http://www.nichd.nih.gov/research/supported/wrhr.cfm
- This example also appears in Chapter 3: *Research Training and Career Development.*
- (E) (**ORWH**, NICHD)

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, SIDS, poor 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. For example, NIH recently created two research networks on premature birth and on stillbirth. The Genomic and Proteomic Network for Premature Birth Research aims to accelerate research in the area of premature birth by providing researchers with the latest technology and methods. The Stillbirth Collaborative Research Network aims to identify the causes of stillbirth so that new interventions can be developed to prevent these tragic outcomes.

- (E) (NICHD)

Prenatal Alcohol, SIDS, and Stillbirth (PASS) Research Network: After a 3-year feasibility study, NIH established this multidisciplinary consortium to determine the role of prenatal alcohol exposure and other maternal risk factors in the incidence and etiology of SIDS, stillbirth, and fetal alcohol syndrome, all of which are devastating pregnancy outcomes. The PASS study will follow 12,000 pregnant, high-risk, American Indian and South African women and their infants prospectively until the infants are 12 months old. Maternal, fetal, and infant measures and tissues will be obtained for analysis.

- http://www.nichd.nih.gov/research/supported/pass.cfm
- (E) (**NICHD**, NIAAA)

Potential Therapy for Children Afflicted with Progeria Syndrome: : Hutchinson-Gilford Progeria Syndrome (HGPS) is a genetic disorder of accelerated aging. In addition to other symptoms of aging, HGPS patients suffer from accelerated cardiovascular disease and often die in their teen or even preteen years from heart-related illnesses. No treatments are currently available for HGPS; however, recent work led by NHGRI researchers indicates that farnesyltransferase inhibitors (FTIs), a class of drugs originally developed to treat cancer by blocking the growth of tumor cells, are capable of reversing the effects of the defective HGPS protein, lamin A. Ongoing studies in a mouse model have validated the results of preliminary experiments, and a clinical trial of FTIs in children with progeria began in 2007. In FY 2008, researchers plan on expanding the study to investigate whether FTIs are

capable of reversing the detrimental effects after progression of the cardiovascular anomalies that are seen in the mouse model. The development of biological assays to assess the effects of FTI treatment on the patients' cells is in progress to monitor the potential beneficial effects of the clinical trial. In addition, it has been demonstrated that the progerin protein is present in small amounts in normal aging tissues. The investigation of this phenomenon is being pursued as a contributory factor to the normal aging process.

- Cao K, et al. Proc *Natl Acad Sci U S A* 2007;104:4949-54, PMID: 17360355
- Capell BC, et al. *Proc Natl Acad Sci U S A* 2005;102:12879-84 PMID: 16129833
- For more information see http://www.genome.gov/10000608
- For more information see http://www.genome.gov/15515061
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Clinical and Translational Research.*
- (I) (NHGRI)

Newborn Screening: Screening and treating newborns for phenylketonuria (PKU) and hypothyroidism have virtually eliminated these conditions as a cause of mental retardation in the United States. A new, trans-NIH collaborative effort will build on this success to develop a new generation of microchips and related technologies that should enable screening programs across the Nation to rapidly test newborns for hundreds of genetic conditions in a single test using one drop of an infant's blood. Complementing the technology development is an initiative to stimulate development of new treatments for such conditions as short chain Acyl CoA dehydrogenase deficiency (SCAD), tyrosinemia, and the genetic causes of hearing loss with the promise of significantly reducing the lifelong health burden of these and other conditions.

- This example also appears in Chapter 3: *Technology Development*
- (E) (**NICHD**, NIDCD, NIDDK)

Discovering the Causes of Nonsyndromic Cleft Lip and Cleft Palate: For nearly 60 years, NIH has supported scientific investigation of causes and interventions for cleft lip and cleft palate, which are among the most common birth defects. In recent years, advances in technology made it possible for scientists to directly sequence genes suspected of contributing to cleft lip and/or palate. NIH grantees and their associates have used this approach to identify genetic mutations accounting for up to 13 percent of cases of cleft lip and/or palate. One of the most recent advances occurred in March 2007, when the scientists reported sequencing the coding regions of 12 members of the fibroblast growth factor (FGF) and FGF receptor gene families and finding seven mutations that may contribute to as much as 5 percent of nonsyndromic cleft lip and/or palate. The group followed up by generating three-dimensional computer models of the FGF proteins that predicted how the altered amino acids would affect their normal shape and function. In a separate finding, NIH-supported scientists reported that women who carry a fetus whose DNA lacks both copies of a gene involved in detoxifying cigarette smoke substantially increase their baby's chances of being born with a cleft lip and/or palate if they smoke. About a quarter of babies of European ancestry and up to 60 percent of those of Asian ancestry lack both copies of the gene, called GSTT1. The scientists calculated that if a pregnant woman smokes 15 cigarettes or more per day, the chances of her GSTT1-lacking fetus developing a cleft increase by nearly 20-fold. Globally, about 12 million women each year smoke through their pregnancies. This finding provides additional motivation for expectant mothers to follow existing advice not to smoke. Other work conducted by NIH scientists looking at occupational exposures of parents suggest that exposures in certain occupations may influence the risk of orofacial clefting in offspring. Specific exposures accompanying these occupations warrant exploration.

- Riley BM, et al. *Proc Natl Acad Sci U S A* 2007;104:4512-7, PMID: 17360555
- Shi M. et al. *Am J Hum Genet* 2007;80:76-90, PMID: 17160896
- Nguyen RH, et al. *Ann Epidemiol* 2007;17:763-71, PMID: 17664071

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E, I) (**NIDCR**, NIEHS)

Craniofacial Birth Defects or Syndromes: Craniofacial defects are among the most common of all birth defects. Birth defects and developmental disorders can be isolated or may be part of complex hereditary diseases or syndromes. Cleft lip and cleft palate are among the more common birth defects in the United States, occurring in about 1 to 2 of 1,000 births. Numerous other disorders with oral and craniofacial manifestations, such as ectodermal dysplasias, Treacher Collins syndrome, and Apert's syndrome, though considerably more rare than cleft lip and cleft palate, also have serious lifetime functional, esthetic, and social consequences. These disorders are often devastating to parents and children alike. Surgery, dental care, psychological counseling, and rehabilitation may help ameliorate the problems, but often at a great cost and over many years. In fact, the lifetime cost of treating the children born each year with cleft lip or cleft palate is estimated to be $697 million. NIH is actively pursuing knowledge to prevent future defects as well as treat those who are currently affected. Exciting advances in genetic studies are shedding light on the genes that are important in forming the head and face, how these genes function, and how they interact with environmental, nutritional, and behavioral factors. Such information may ultimately provide the knowledge necessary for prenatal diagnosis, the development of methods to prevent craniofacial birth defects, and the basis for developing better treatments. The development of biocompatible, naturally derived materials and biodegradable scaffolds offers new hope for the treatment of defects resulting from craniofacial birth defects or syndromes.

- For more information, see http://www.cdc.gov/mmwr/preview/mmwrhtml/00038946.htm
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development.*
- (E, I) (**NIDCR**, NIEHS)

Understanding the Causes and Conceiving New Treatments for Craniosynostosis: Craniosynostosis arises when one or more of the fibrous sutures between the six cranial bones prematurely fuse and lock sections of the skull tightly into place. Because the brain continues to grow during early childhood, craniosynostosis, if left untreated, can distort the shape of the skull and portions of the face, as well as cause hearing loss, blindness, and/or intellectual disability. To better understand the causes of craniosynostosis, a team of NIH-supported researchers study the fusion of cranial sutures in mice. They suspect that the premature fusion involves alterations in the normal biochemical interplay between embryonic tissue, called mesenchyme, from which the cranial sutures form, and a thin fibrous layer of tissue, called the dura mater, that lies beneath it. The scientists also have found that different regions of the dura mater send different developmental signals to the overlying mesenchyme. Defining in fine detail the signals between the mesenchyme and the dura mater could provide the intellectual basis for discovering and developing noninvasive biological approaches to control craniosynostosis. NIH-supported researchers have made an important step in this direction. They isolated mesenchymal cells derived from cranial sutures in two different areas of the skull, cultured each group of cells separately, and later analyzed their gene expression patterns. The scientists found clear differences in the patterns of genes expressed among the two populations of mesenchymal cells. To their knowledge, this marks the first glimpse of the genetic programs that are wired into mesenchymal cells derived from cranial sutures. This line of research potentially opens a new chapter in understanding the causes of and conceiving new treatments for cranial synostosis.

- Xu Y, et al. *Plast Reconstr Surg* 2007;119:819-29, PMID: 17312483
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NIDCR)

Cesarean Delivery Versus Vaginal Birth: The rate of cesarean delivery has risen dramatically over the past two 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. Among other findings, the registry data showed that women who gave birth to a child vaginally, after a previous cesarean delivery of twins or triplets, were not at higher risk for complications during labor and delivery.

- *NIH Consens State Sci Statements.* 2006;23:1-29, PMID: 17308552
- Varner M for the NICHD MFMU Network, The MFMU Cesarean Registry: VBAC success and complication rates following one previous cesarean for multifetal gestation. Abstract for the Society for Maternal-Fetal Medicine Annual Meeting 2006.
- (E) (NICHD)

Maternal Oral Health and Obstetric Outcomes: In recent years, evidence has suggested that a pregnant woman with periodontal (gum) disease might be at increased risk for premature birth. Two similar but not identical NIH-supported trials evaluate this possibility. Conducting more than one large clinical trial on this important public health question will cast a wide enough investigational net to determine which, if any, women are at risk. One study, called the Obstetrics and Periodontal Therapy Trial (OPT), recently concluded that periodontal treatment during pregnancy is safe for mother and baby but does not significantly lower preterm birth risk. The Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR) study is ongoing.

- For more information see http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/NRY2006/PR11012006.htm
- For more information see http://www.nidcr.nih.gov/Research/ResearchResults/InterviewsOHR/TIS072005
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- **(E) (NIDCR)**

Study Shows Child's Weight Can Be Influenced by Mother Before and During Pregnancy: NIH-supported researchers found that a child's weight may be influenced by its mother even before the child is born. In a study of more than 3,000 children, scientists found that children of mothers who were obese before pregnancy were more likely to be overweight by 3 years of age. In addition, children born to African American or Hispanic mothers or to mothers who smoked during pregnancy were at greater risk for becoming overweight. These findings indicate the need to develop creative and effective strategies to promote healthy nutritional habits in prospective mothers as a way of reducing later health problems in their children.

- Reagan PB, Salsberry PJ. *Soc Sci Med* 2005;60:2217-28, PMID: 16322155
- For more information, see see http://www.nih.gov/news/pr/dec2005/ninr-05.htm
- (E) (NINR)

NICU Program Reduces Premature Infants' Length of Stay and Improves Parents' Mental Health Outcomes: In a randomized, controlled clinical trial, NIH-funded investigators tested an educational program, called Creating Opportunities for Parental Empowerment (COPE), among parents of premature infants. An estimated half a million premature infants are born in the United States each year. Most require hospitalization in a newborn intensive care unit, and their parents often suffer high levels of stress, anxiety, and depression. Compared with controls, parents who participated in the COPE program reported better understanding of the behaviors to expect from their infants and displayed more positive parent-infant interactions. Mothers had lower anxiety, depression, and

overall parenting stress, and fathers were more involved in the infants' care. Infants of COPE parents averaged 3.8 fewer days in the neonatal intensive care unit than the control infants, which translated to a savings of roughly $5,000 per infant.

- Melnyk BM, et al. *Pediatrics* 2006;118:e1414-27, PMID: 17043133
- For more information, see http://www.nih.gov/news/pr/nov2006/ninr-01.htm
- (E)(NINR)

Trial to Reduce the Incidence of Type 1 Diabetes for Those Genetically at Risk (TRIGR): Researchers are conducting a study to determine whether the onset of type 1 diabetes mellitus can be delayed or prevented by weaning genetically susceptible infants to Nutramigen®, a hydrolysate of cow milk protein, instead of to a standard cow milk-based infant formula. Earlier studies in animal models have shown that hydrolyzed protein diets prevented the onset of type 1 diabetes. TRIGR is the first large effort designed to ascertain whether a simple nutritional intervention during infancy can delay or prevent the onset of type 1 diabetes in children who are at high genetic risk for the disease. Enrollment for the study was recently completed, totaling more than 2,000 children from 15 countries.

- For more information, see http://www.nichd.nih.gov/research/supported/TRIGR.cfm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*
- (E) (**NICHD**; NIDDK administers the contribution from the special statutory funding program for type 1 diabetes)

Childhood and Maternal Obesity: As the maternal and childhood obesity epidemic grows, 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 topics such as:

- Basic research on the physiology, psychology, and genetics of obesity in children
- Developing working definitions of the metabolic syndrome in children and adolescents
- Linking maternal obesity, reproductive health, and pregnancy to adverse health outcomes
- Behavioral intervention trials in schools, the home, and the community

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E, I) (**NICHD**, NCCAM, NCI, NCMHD, NHLBI, NIDCR, NIDDK, NINR, OBSSR, ODP)

Diabetes Research in Children Network (DirecNet): The risk of hypoglycemia is now the main obstacle to successfully managing type 1 diabetes mellitus in children of all ages. Severe hypoglycemia can lead to seizures or unconsciousness. In 2001, NIH established DirecNet to assess the accuracy and efficacy of continuous glucose monitoring devices, evaluate the effectiveness of the devices as tools to help control blood sugar levels, and determine the incidence of hypoglycemia. DirecNet also focuses on possible changes in neurocognitive function in children with type 1 diabetes who have frequent bouts of hypoglycemia. The network was recently renewed to use new tools to evaluate factors and mechanisms contributing to hypoglycemia, such as exercise and diet. The goal is to continue to improve management of type 1 diabetes and prevent hypoglycemia by “closing the loop” between measuring glucose levels and delivering insulin.

- For more information, see http://www.nichd.nih.gov/research/supported/directnet.cfm
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-06-020.html
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Technology Development.*

- (E) (**NICHD**, NIDDK, NINDS)

HEALTHY: The HEALTHY multicenter clinical trial aims 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 three major risk factors for 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. In the full-scale HEALTHY trial, 42 enrolled middle schools receive the intervention, which includes changes to school food service and physical education classes, behavior change, and communications campaigns. More than 80 percent of the enrolled students are from minority populations.

- For more information, see http://www.nih.gov/news/pr/aug2006/niddk-28.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*
- (E) (NIDDK)

Studies of Diabetes in Youth: Previously known as a disease of adults, type 2 diabetes is increasingly being observed in youth. The Treatment Options for Type 2 Diabetes in Youth study is comparing three different treatment strategies for children with the disease. The SEARCH for Diabetes in Youth Study is providing key data on childhood diabetes incidence and prevalence. SEARCH estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. Although type 2 diabetes is increasing in children over 10, particularly minorities, type 1 diabetes accounts for most new cases, with an estimated 15,000 youths diagnosed annually.

- For more information, see http://www.todaystudy.org/index.cgi
- For more information, see http://www.searchfordiabetes.org
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIDDK**, CDC)

The Environmental Determinants of Diabetes in the Young: Understanding the environmental factors, such as infectious agents or diet, that can trigger type 1 diabetes in genetically susceptible individuals is crucial to developing prevention strategies. To address this knowledge gap, NIH established The Environmental Determinants of Diabetes in the Young (TEDDY) consortium. This international consortium is enrolling newborns and following them until age 15 to identify environmental triggers for type 1 diabetes. The study is amassing the largest set of data and samples in the world for newborns at risk for type 1 diabetes.

- For more information, seehttp://teddy.epi.usf.edu
- This information also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (**NIDDK**, NIAID, NIEHS, CDC, and the Juvenile Diabetes Research Foundation)

Longitudinal Assessment of Bariatric Surgery (LABS): The multicenter, NIH-funded LABS consortium is analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity in adults. Because bariatric surgery is also sometimes used in clinical practice as a treatment for severely obese adolescents, NIH is also 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.

- For more information, see http://tinyurl.com/399zmt
- http://tinyurl.com/yoer3l
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*

- (E) (**NIDDK**, ORWH)

Bone Health: NIH researchers established reference curves for bone mineral content and density in children. The early findings are now available according to age, sex, and race and can be used to help identify children with bone deficits and to monitor changes in bone in response to chronic diseases or therapies. Early study findings showed that bone minerals continue to accrue beyond the teenage years, so the study will continue as the adolescent participants approach young adulthood. In another study, NIH scientists discovered two genes for osteogenesis imperfecta, or brittle bone disease. The genes affect how collagen, an important building block for bone, is formed. Although there is no treatment for the disorder, the findings allow researchers to test families who have lost a child to osteogenesis imperfecta for the presence of the defective genes.

- Kalkwarf HJ, et al. *J Clin Endocrinol Metab* 2007;92:2087-99, PMID: 17311856
- Barnes AM, et al. *N Engl J Med* 2006;355:2757-64, PMID: 17192541
- Cabral WA, et al. *Nat Genet* 2007;39:359-65, PMID: 17277775
- (E, I) (NICHD)

Never Too Early—The Milk Matters Campaign: The risk for osteoporosis actually starts in childhood. Thus, NIH supports a public health campaign to help increase calcium consumption among children and teens, ages 11 to 15, a time of critical bone growth. Milk Matters is designed to educate parents, teachers, and health care providers about how most tweens and teens are not getting enough calcium their diets. The campaign features materials and publications in English and Spanish.

- For more information, see http://www.nichd.nih.gov/milk/milk.cfm
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (**NICHD**, NIDCR)

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 and science. NIH's long-standing research efforts on individual differences in learning, how children learn to read, and specific learning disabilities enable it to play a leading role in improving understanding and developing these interventions. For example, NIH Mathematics and Science Cognition and Learning program supports both basic and intervention research in all aspects of mathematical thinking and problem solving, as well as in scientific reasoning, learning, and discovery. In partnership with the Department of Education, 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.

- (E) (NICHD)

Intellectual and Developmental Disabilities: Intellectual and developmental disabilities have serious, lifelong effects on cognitive and adaptive development. NIH supports research to improve functioning for individuals who have intellectual and development disabilities and to understand the underlying genetic processes to prevent these conditions. For example, NIH supports 14 Mental Retardation/Developmental Disabilities Research Centers to advance diagnosis, prevention, treatment, and amelioration of intellectual and developmental disabilities. 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 Research Centers, Rare Disease Cooperative Centers, and Autism Centers. In addition to these centers, NIH supports research to better understand the neurobiology and genetics that underlie the cognitive and behavioral processes in persons with Down's syndrome and other intellectual and developmental disabilities.

- For more information, see http://www.nichd.nih.gov/about/org/cdbpm/mrdd/supported/index.cfm
- (E) (NICHD)

National Database for Autism Research (NDAR): The NDAR is a collaborative biomedical informatics system being created by NIH to provide a national resource to support and accelerate research in autism.

- 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.*
- (I, E) (**NIMH**, NICHD, NINDS, NIEHS, NIDCD, CIT)

Teen Driving: Over one-third of teenage deaths are due to motor vehicle accidents. NIH-supported researchers recently completed a study demonstrating that teen drivers' behavior often became more risky in the presence of teen passengers. The researchers found that teenage drivers—both males and females—were more likely to tailgate and exceed the speed limit if there was a teenage male passenger in the front seat. Conversely, male teenagers were less likely to tailgate or exceed the speed limit when a teenage female was in the front passenger seat. To determine why the presence of teen passengers influenced these behaviors, NIH researchers are designing a study that will involve placing electronic monitoring equipment in vehicles with teen drivers. After learning the specific reasons for the risky behavior, researchers can then work to develop ways to prevent it.

- Simons-Morton B, et al. *Accid Anal Prev* 2005;37:973-82, PMID: 15921652
- (I) (NICHD)

Underage Drinking Research Initiative: In 2004, NIH launched this ongoing 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 development. Activities and achievements in 2007 include:

- Provided the scientific foundation for The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking (released March 6, 2007) and for the ongoing work of the Interagency Coordinating Committee on Preventing Underage Drinking
- Convened scientific meetings of experts, including the Underage Steering Committee, which met four times over a 2-year period; a Meeting on Diagnosis of Alcohol Use Disorders among Youth (April 2006); and a Meeting on Screening for Child and Adolescent Drinking and AUDs among Youth (June 2007)
- Issued three RFAs, including “Underage Drinking: Building Health Care System Responses” (four projects awarded in FY 2006), “Impact of Adolescent Drinking on the Developing Brain” (five projects awarded in FY 2007), and “Alcohol, Puberty and Adolescent Brain Development” (three projects awarded in FY 2007)
- Published *Alcohol Research and Health,* Volume 28, Number 3, “Alcohol and Development in Youth: A Multidisciplinary Overview”
- Published a supplement of seven developmentally focused papers covering a broad range of underage drinking topics (accepted for the journal Pediatrics).

- For more information, see http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm
- (E) (NIAAA)

The Rapid Response Program: In April 2002, the Task Force on College Drinking released its seminal report, "A Call to Action: Changing the Culture of Drinking at U.S. Colleges." As part of its college focus, NIH initiated support of collaborations between university personnel who have responsibility for alcohol programs on various campuses and established college drinking researchers to implement and evaluate programs to reduce underage alcohol use and its consequences. These programs include:

- RFA AA-03-008: "Research Partnership Awards for Rapid Response to College Drinking Problems." Five U01 (cooperative agreement) 5-year grants were awarded in December 2002.
- PAR-03-133: "Rapid Response to College Drinking Problems. " Fifteen 3- year grants were awarded in June 2003. This rapid funding mechanism (U18, cooperative agreement) supports timely research on interventions to prevent or reduce alcohol-related problems among college students. It was intended to support studies of services or interventions that could capitalize on "natural experiments" (e.g., unanticipated adverse events, policy changes, new media campaigns, campus-community coalitions, etc.). Each U18 grantee was required to partner with a U01 grantee. Together, these pairs, working with NIH Scientific Staff Collaborators, jointly design, develop, implement, and evaluate college drinking projects on their campuses.

    - This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
    - (E) (NIAAA)

Adolescent Medicine Trials Network for HIV/AIDS Interventions (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 impact the transmission dynamics 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 youth and those at risk of infection. Researchers in this network are building the capacity to develop and conduct selected biomedical, behavioral, and community-based studies, including vaccine and microbicide trials to ensure that the needs of high-risk teens are considered as treatment and prevention interventions are being developed.

- For more information, see http://www.atnonline.org
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense.*
- (E) (**NICHD**, NIDA, NIMH)

Adolescent Depression and Suicide: NIH continues to support research on the treatment of depression during adolescence, including the concern that certain antidepressant medications, called selective serotonin reuptake inhibitors, can increase the risk of suicide. NIH supported a recent meta-analysis of studies on this subject that found that the benefits of antidepressant medication for children and adolescents with major depressive disorder and anxiety disorders likely outweighed any potential risks.

- For more information see http://www.nimh.nih.gov/healthinformation/antidepressant_child.cfm
- (E) (NIMH)

Interventions and Services for Youth with Mental Illness Who Are Transitioning to Adulthood: The transition to adulthood for youth with mental illness is often a period in which care is compromised, with a host of negative outcomes. In 2006, NIH launched an initiative to stimulate research on refining and testing interventions in service delivery models for youth transitioning to adulthood. Four applications were funded.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-07-050.html
- http://www.nimh.nih.gov/science-news/2007/new-research-to-help-youth-with-mental-disorders-transition-to-

adulthood.shtml

- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NIMH)

Alzheimer's Disease Neuroimaging Initiative (ADNI): ADNI is an innovative public-private partnership for examining the potential for serial MRI, PET, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease. Early results suggest that researchers may be able to reduce the costs associated with clinical trials by improving imaging and biomarker analysis. One ADNI study found that a standard model can be used to monitor the performance of MRI scanners at multiple clinical sites, ensuring the accuracy of the MRI images. In another study, investigators compared changes over time in PET scans of brain glucose metabolism in people with normal cognition, mild cognitive impairment, and Alzheimer's disease and found that scans correlated with symptoms of each condition and that images were consistent across sites, suggesting the validity of PET scans for monitoring the effectiveness of therapies in future clinical trials. More than 200 researchers have already accessed a public database containing thousands of brain images and related clinical data obtained through blood and cerebrospinal fluid analyses.

- For more information, see http://www.loni.ucla.edu/ADNI
- (E) (**NIA**, NIBIB)

Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE): This recent multicenter study in community-dwelling seniors showed that certain mental exercises can offset expected declines in thinking skills of older adults and show promise for maintaining the cognitive abilities needed for tasks such as shopping, making meals, and handling finances. The ACTIVE study is the first randomized, controlled trial to demonstrate long-lasting, positive effects of brief cognitive training in older adults. Although training did not improve the participants' ability to tackle other everyday tasks, their cognitive skills declined less than with untrained seniors. Additional research is needed to translate these findings from the laboratory into interventions that prove effective at home.

- For more information, see http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20061219ACTIVE.htm
- (E) (NIA)

Lifestyle Interventions and Independence for Elders: Results of several studies have suggested that physical exercise may prevent physical disability, including impaired mobility, in both healthy and frail older adults. To develop definitive evidence regarding the effectiveness of such interventions, NIH designed the Lifestyle Interventions and Independence for Elders (LIFE-P) pilot study, a clinical trial that tested the effects of a physical activity program versus a health education program in preventing major disability. The study involved 424 participants age 70 to 89 who were at risk of disability. These individuals were followed for at least 1 year at four locations around the country: Wake Forest University School of Medicine in Winston Salem, North Carolina; the University of Pittsburgh in Pennsylvania; the Cooper Institute in Dallas, Texas; and Stanford University in Palo Alto, California. At various points in the physical exercise intervention, study participants were tested for their performance on a battery of lower-extremity function tests and the time required for them to walk 400 meters. At the end of the study, participants in the intervention group demonstrated significant improvement over controls. This successful pilot study was completed in 2005 and showed both feasibility and positive preliminary data to permit the design and consideration of a large-scale clinical trial.

- (I, E) (NIA)

Inflammation in the Elderly: Inflammatory processes, particularly those mediating chronic inflammation, have

been implicated as predictors or initiators of or contributors to a number of chronic diseases and conditions of aging. NIH currently supports research to determine relationships of age-related changes in inflammation and inflammatory mediators to physiologic and pathophysiologic aging changes, risks and progression of age-related morbidity and disability, and changes in tissue and organ function. Funded projects include studies of vascular inflammation and neurotoxicity in the aging brain and inflammatory responses to sleep loss.

- For more information, http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-05-011.html
- (E) (NIA)

Neuroeconomics of Aging: Scientists in the emerging field of neuroeconomics seek to explain the psychological mechanisms that guide economic decisions and the neurobiological pathways that underlie them. NIH is currently supporting research to examine the social, emotional, cognitive, and motivational processes and neurobiological pathways of economic behavior as they (1) influence social, financial, and health-related decisions affecting the well-being of middle-aged and older adults and (2) inform the development and refinement of integrative economic theories of utility, learning, and strategic choice relevant to aging.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-06-011.html
- (E) (NIA)

National Long-Term Care Survey (NLTCS): NLTCS is an ongoing longitudinal study supported by NIA to examine changes in the health and functional status of older Americans and track health expenditures. The study is one of the Nation's preeminent resources for understanding and analyzing national disability trends and other demographic trends to inform public health policy. Efforts are currently under way to make the d ata publicly available.

- http://www.nltcs.aas.duke.edu/index.htm
- (E) (NIA)

Improving Communication About End-of-Life Care in the ICU Reduces Symptoms of Stress, Anxiety, and Depression in Family Members: A clinical trial supported in part by NIH found that an intervention to improve communication between intensive care unit clinicians and family members of a dying patient significantly reduced feelings of stress, anxiety, and depression in the family members. In the randomized controlled trial, researchers examined communication guidelines that follow the mnemonic VALUE: to Value what the family members said, Acknowledge their emotions, Listen, Understand the patient as a person, and Elicit family member questions. From interviews conducted 3 months after the death of the patient, family members in the VALUE group were found to have lower scores for stress, anxiety, and depression than those in the customary-practice group. The finding indicated that improving communication in end-of-life family conferences in the intensive care unit helped family members express their views and emotions, accept a more realistic goal of care, and improve their long-term psychological outcomes.

- Lautrette A, et al. *N Engl J Med* 2007;356:469-78, PMID: 17267907
- For more information, see http://www.nih.gov/news/pr/feb2007/ninr-01.htm
- (E) (NINR)

Improving End-of-Life Care: Special Supplement to the Journal of Palliative Medicine: FY 2005, NIH sponsored the State-of-the-Science Conference on Improving End-of-Life Care. This conference addressed the current state of end-of-life care and proposed important new directions for end-of-life research. Key conclusions to emerge from the conference included: the rapid increase in older adults facing the need for end-of-life care requires the

development of research infrastructure to better examine end-of-life issues; enhanced communication between patients, families, and providers is crucial to end-of-life care; and improved outcome measures are needed to better conduct end-of-life research. In FY 2006, a special issue of the Journal of Palliative Medicine presented a series of papers developed from this workshop on a wide variety of topics. The supplement includes articles on measuring end-of-life care outcomes; analyzing racial, cultural, and ethnic factors that influence end-of-life care; improving care for dying children and their families; and examining factors in the health care system that influence end-of-life care.

- Grady PA. *J Palliat Med* 2005;8:S1-3, PMID: 16499457
- For more information, see http://www.liebertonline.com/toc/jpm/8/supplement+1
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*
- (E) (NINR)

Centers in Self-Management or End-of-Life Research: Future progress in improving the ability of those with chronic disease at all stages of life to manage their own illness, as well as improving the care of patients at the end of life, will require the development of enhanced research capacity, in terms of both people and institutions. In early 2007, NIH solicited applications for the Centers in Self-Management or End-of-Life Research. These Centers are expected to enhance research and training capacity for interdisciplinary, biobehavioral efforts in end-of-life and self-management science.

- 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)

Rehabilitation Research

Neural Prosthesis Program: 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. The NINDS Neural Prosthesis program pioneered the development of this technology beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants for the hearing impaired, respiratory and hand grasp devices for people with spinal cord injuries, and deep brain stimulation for patients with Parkinson's disease, among other contributions. Current work aims to restore standing and voluntary bowel and bladder control after spinal cord injury, to allow paralyzed persons to control devices directly from their brains, and to control seizures. Ongoing research also seeks to improve cochlear implants and to advance 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 NIH Institutes, which coordinate their efforts with programs now under way in the Department of Veterans Affairs and DoD.

- 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**, NIBIB, NIDCD, NICHD, NEI)

Upper Limb Rehabilitation: To improve the process of restoring function in the upper limbs, NIH is developing robotic exoskeletons for rehabilitation of upper-extremity paralysis. Recent studies demonstrate that practicing tasks repetitively with feedback can enhance recovery of arm function for selected populations of stroke survivors.

This type of practice typically requires the assistance of a trained physical therapist. However, the development of low-cost robotic exoskeletons holds the promise of providing therapeutic activities at home and in a variety of settings to help a wider range of stroke patients improve functioning more efficiently.

- (E) (**NICHD**, NIBIB) (GPRA Goal)

High-Tech Replacements for Damaged Limbs: NIH is investing strategically to develop improved prosthetic devices that can help soldiers and other individuals who have lost limbs resume normal activities. The latest developments and research activities include a new, "intelligent" artificial knee joint that enables a user's lower-leg prosthesis to adjust automatically to hills, stairs, and other variable surfaces, offering greater mobility. Scientists are also working on developing a prototype "bionic arm," controlled by microprocessors that read signals through nerves that have been rerouted from the neck to the chest. Investigators are also seeking ways to implant an artificial limb directly into the bone of the residual limb, doing away with the need for a socket device, which often causes painful, chronic irritation.

- Johansson JL, et al. *Am J Phys Med Rehabil* 2005;84:563-75, PMID: 16034225
- Kuiken TA, et al. *Lancet* 2007;369:371-80, PMID: 17276777
- Pitkin M, et al. *J Rehabil Res Dev* 2006;43:573-80, PMID: 17123195
- (E) (NICHD)

New Medical Adhesive Boasts Unique Wet-Dry Abilities: One day, tissue engineering will make it possible to regenerate lost facial components. Until then, victims of massive craniofacial trauma or extensive surgeries due to cancer often must depend on maxillofacial prosthetics to provide the form and function needed to resume their day-to-day lives. Current adhesives are not always retentive over long periods or changing conditions. The loss of retention can result in visible margins or even dislodgement of the prosthesis. Now NIH-supported scientists report they have merged two of nature's most elegant strategies for wet and dry adhesion. As reported in Nature, the scientists designed a synthetic material that starts with the dry adhesive properties of the gecko lizard and supplements it with the underwater adhesive properties of a mussel. The hybrid material, which they call a geckel nanoadhesive, proved in initial testing to be adherent under dry and wet conditions and also adhered much longer under both extremes than previous gecko-based synthetic adhesives, a major issue in this area of research. According to the authors, their findings mark the first time that two polar opposite adhesion strategies in nature have been merged into a manmade reversible adhesive. It is envisioned that the new adhesive will be used for many medical applications, including enhancing the retention of oral and maxillofacial prosthetics.

- Lee H, et al. *Nature* 2007;448:338-41, PMID: 17637666
- For more information see http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/NRY2007/PR07182007.htm
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*.
- (E) (NIDCR)

Engineering Stem Cells to Repair or Replace Damaged Tissues: Guiding a person's own stem cells to repair or replace damaged tissues with healthy tissue is the goal of multiple NIH-supported tissue engineering projects. For example, one team previously reported success creating three-dimensional mandibular (jaw) joints using rodent tissue; their continuing work on the project addresses pragmatic questions that must be answered in order to create functional human joints. Other teams are working on regeneration of the temporomandibular disk, which acts as a cushion between the bony components of the jaw joint and on the tissue engineering of skeletal muscle. Tissue engineering holds great promise for regeneration or replacement of dental, oral, and craniofacial structures lost due to trauma, disease, or congenital anomalies. The progress seen in this area will also inform tissue

engineering solutions for degeneration in other articular surfaces, such as knee, hip, and shoulder joints.

- Mao JJ, et al. *J Dent Res* 2006;85:966-79, PMID: 17062735
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NIDCR)

Maintaining Physical Function in Older Populations: Chronic disability among older Americans has dropped dramatically, and the rate of decline has accelerated during the past two decades, according to recent analysis of data from the NIH National Long-Term Care Survey (NLTCS), which examined disability changes within three age groups (65-74, 75-84, and 85+) and found that the prevalence of chronic disability among people age 65 and older fell from 26.5 percent in 1982 to 19 percent in 2004/2005. The proportion of people without disabilities increased the most in the oldest age group, rising by 32.6 percent among those age 85 and older. The findings suggest that older Americans' health and function continue to improve at a critical time in the aging of the population. The question of how best to maintain and accelerate the trend of declining disability, especially in the face of increasing rates of obesity, will be addressed at a workshop sponsored by the National Academies and commissioned by NIH. NIH currently supports large, multidisciplinary research programs that focus, in part, on rehabilitation research for older people. For example, one of the Claude D. Pepper Older Americans Independence Centers conducts exercise and motor learning-based rehabilitation research to optimize the recovery of older adults who have suffered a stroke, hip fracture, or other chronic debilitating disease and translate these findings into effective community-based rehabilitation programs (see Chapter 4). The Edward R. Roybal Centers for Applied Gerontology conduct applied research to keep older persons independent, active, and productive in later life.

- Manton KG, et al. *Proc Natl Acad Sci U S A* 2006;103:18374-9, PMID: 17101963
- (E) (NIA)

International Collaborative Trauma and Injury Research Training Program: Each year, more than 5 million deaths and countless disabilities result from injuries. This program is strengthening the scientific expertise in developing countries in human injury-related research and funds 11 collaborations between institutions in high-income countries and low- or middle-income countries. These collaborations support research training in applied science, the epidemiology of risk factors, acute care and survival, rehabilitation, and long-term mental health consequences of trauma and injury. The program is also supported by the World Health Organization, the Pan American Health Organization, and CDC.

- For more information, see http://www.fic.nih.gov/programs/training_grants/trauma/index.htm
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (FIC)

Cochlear Implants: One of the more groundbreaking biomedical achievements in the last 30 years has been the cochlear implant, an electronic device that provides a sense of sound to individuals who are profoundly deaf or severely hard-of-hearing. Cochlear implants process sounds from the environment and directly stimulate the auditory nerve, bypassing damaged portions of the inner ear. Nearly 100,000 individuals worldwide have been fitted with cochlear implants. In the United States, approximately 22,000 adults and nearly 15,000 children have received them. Derived in part from NIH-funded research that dates back to the early 1970s and continues today, this remarkable technology has enabled deaf and severely hard-of-hearing individuals to enjoy an enhanced quality of life. NIH-supported scientists showed that profoundly deaf children who receive cochlear implants at an early age develop language skills at a rate comparable to that of children with normal hearing. They also found that the benefits of the cochlear implant in children far outweigh its costs. Scientists can now study the large groups of

children who were identified early for hearing loss and use this knowledge to document how treatments such as cochlear implants can lead to improved speech and language acquisition, academic performance, and economic outcomes for these children.

- Nicholas JG, Geers AE. *Ear Hear* 2006;27:286-98, PMID: 16672797
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development.*
- (E) (NIDCD)

NIH Strategic Plans Pertaining to Life Stages, Human Development, and Rehabilitation Research

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

- *From Cells to Selves Strategic Plan for the NICHD, 2000*
- *Reproductive Health for the 21st Century, 2001*
- *Developmental Biology, 2001*
- *Genetics and Fetal Antecedents of Disease Susceptibility, 2001*
- *Biobehavioral Development, 2001*
- *Targeting Sudden Infant Death Syndrome (SIDS): A Strategic Plan, 1995, 1998, 2001*
- *Demographic and Behavioral Sciences Branch Goals and Opportunities, 2002-2006*
- *Pregnancy and Perinatology Branch Strategic Plan, 2005-2010, 2003*

Branch Reports to Council with Future Scientific Directions:

- *Mental Retardation and Developmental Disabilities (MRDD) Branch, Report to the NACHHD Council, June 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*
- *Pediatric, Adolescent, and Maternal AIDS Branch (PAMAB), NICHD, Report to the NACHHD Council, June 2007*
- *Reproductive Sciences Branch, NICHD Report to the NACHHD Council, January 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*

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 on Aging (NIA)

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

National Institute on Drug Abuse (NIDA)

- *NIDA Draft Strategic Plan*

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)

- *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)

Summary of Research Activities by Disease Categories

Minority Health and Health Disparities

The Medical Committee for Civil Rights (later the Medical Committee for Human Rights) was formed in the early 1960s and participated in the 1963 March on Washington, where Dr. Martin Luther King gave his famous "I have a dream" speech. The group succeeded in highlighting racial inequalities in American medicine during a time when racial segregation in professional medical associations, hospitals, and medical education was commonplace. It was at the second National Convention of the Medical Committee for Human Rights that Dr. King made a less well-known but equally profound speech, stating, "Of all the forms of inequality, injustice in health is the most shocking and the most inhumane."

Introduction

Despite remarkable progress in the biomedical sciences in recent years—understanding diseases and their mechanisms and enhancing the ability to prevent, diagnose, and treat disease—significant segments of the U.S. population still are more likely than others to suffer elevated morbidity and mortality and disproportionate incidence of diseases and adverse outcomes such as cancer, cardiovascular disease, diabetes, HIV/AIDS, and infant mortality. Collectively, the term *health disparity populations* refers to racial and ethnic minorities (African Americans, Hispanics, American Indians, Alaska Natives, Asian Americans, Native Hawaiians and other Pacific Islanders) and medically underserved populations, including individuals of low socioeconomic status and those living in rural areas.

Characterization of the root causes of these health disparities has been and will continue to be the focus of considerable NIH research. As results of investigations in this area have been published over the years, a broad-brush portrait has begun to emerge of the overall causal factors contributing to the creation and persistence of health disparities. It is clear at this point that these problems are often complex and multifactorial—the unfortunate end results of an interwoven and sometimes overlapping array of disparate factors, including societal, biological, behavioral, and environmental effects. For example, studies have shown that poverty and lack of education correlate with poor health and reduced life expectancy. There is well-documented evidence that discrimination based on racial, ethnic, and linguistic differences persists in the United States and has been shown to be a biological stressor as well as an ongoing barrier to access to and quality of health care. Those barriers all too often coalesce with lack of access to health care or access only to substandard health care. In addition, some racial and ethnic minority groups are genetically susceptible to certain diseases, and this places them at increased risk when such inherited biological vulnerabilities combine with adverse social and environmental factors (e.g., poor diet, chemical exposures, economic stress). These are but a few of the many interrelated factors that contribute to the existence of unacceptable health disparities in the United States, which emphasizes the need for population research.

Thus, as the U.S. population in general has become significantly healthier in recent decades, too many individuals have continued to suffer poor health, disability, and/or premature death due to factors beyond their immediate control and conditions beyond their personal choice. Overcoming health disparities is the Nation's foremost health challenge—a formidable challenge, no doubt, but one that can and will be met through gains in knowledge and the application of that knowledge in forthright, effective interventions.

In keeping with its role as the steward of medical and behavioral research for the Nation, NIH is firmly committed to reducing and ultimately eliminating health disparities in the United States. To achieve the vision of a time when all have the opportunity for long, healthy, and productive lives, NIH incorporates the goals of improved minority health and reduced health disparities in its support of biomedical and behavioral research, research training, research capacity, outreach, and research information dissemination.

Many of these activities are multidisciplinary collaborations involving several ICs, the entire NIH, or NIH working with other entities. Efforts are guided by the *NIH Health Disparities Strategic Plan, Fiscal Years 2004-2008*, a comprehensive, continuously evolving document that sets the overarching health disparities agenda for the entire agency. The plan, approved by the National Advisory Council on Minority Health and Health Disparities but awaiting formal clearance, 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 competent workforce; and (3) to engage in aggressive, *proactive community outreach, information dissemination, and public health education*. All NIH ICs have a minority health/health disparities strategic plan, and those plans are captured within the NIH-wide plan. NCMHD takes the lead on NIH's health disparities agenda related to those three goals.

Established in 2000 to conduct and support research, training, dissemination of information, and other programs with respect to minority health conditions and other populations with health disparities, NCMHD's mission is to promote minority health and to lead, coordinate, support, and assess NIH efforts to eradicate health disparities. For example, NCMHD supports 76 Centers of Excellence across the Nation devoted to health disparities research, training, and outreach and has supported more than 400 collaborative research projects by creating partnerships with ICs and other agencies within HHS.

Burden of Illness and Related Health Statistics

Ongoing health disparities affecting racial and ethnic minorities are well documented and are seen in a broad spectrum of diseases and adverse outcomes. The findings consistently have shown that minorities are less likely than Whites to receive needed services, including clinically necessary procedures. These disparities are sometimes associated with socioeconomic differences and tend to diminish significantly and, in a few cases, disappear altogether when socioeconomic factors are controlled. However, some racial and ethnic disparities remain even after adjustments are made for socioeconomic differences and other factors related to health care access[94].

Despite remarkable reductions in cardiovascular morbidity and mortality over the past four decades, minorities still bear a disproportionate share of the burden. Heart disease rates have been consistently higher for the African American population than for Whites. In 2004, heart disease age-adjusted death rates for African American men (342.1 per 100,000) and African American women (236.5 per 100,000) were 30 and 37 percent higher than for White men and women, respectively[95]. Similarly, in the period 1999-2004, stroke affected 3.4 percent of the African American population under 75 years old, versus 1.9 percent of Whites under 75[96]. Stroke mortality in that

---

[94] *Institute of Medicine. The Unequal Burden of Cancer: An Assessment of NIH Research and Programs for Ethnic Minorities and the Medically Underserved*. Washington, DC: National Academy Press, 1999.

[95] For more information, see http://www.cdc.gov/nchs/data/hus/hus06.pdf

[96] For more information, see http://www.nhlbi.nih.gov/resources/docs/cht-book.htm

age group was two to three times higher in African Americans than in Whites[97]. Death certificate data from 2002 showed that mean age at stroke death was younger among African Americans, American Indians/Alaska Natives, and Asians/Pacific Islanders than among Whites and was also younger among Hispanics than non-Hispanics[98].

Cancer deaths vary by gender, race, and ethnicity, but certain racial and ethnic groups have been shown to have lower survival rates than Whites for most cancers. For example, colorectal cancer incidence and death rates are higher among African Americans than among Whites. African American men have the highest rates of prostate, lung, colon/rectum, and oropharyngeal cancers[99].

African Americans comprised approximately 13 percent of the U.S. population but accounted for 49 percent of the estimated 38,096 new HIV/AIDS diagnoses in 2005 in the 33 states with long-term, confidential name-based HIV reporting. In 2005, HIV/AIDS rates were 72.8 per 100,000 among African Americans, 28.5 among Hispanics, 10.6 among American Indians/Alaska Natives, 9.0 among Whites, and 7.6 among Asians/Pacific Islanders[100].

In 2004, infant mortality rates showed a persistent disparity between African Americans (13.7 deaths per 1,000 live births) and Whites (5.7 deaths per 1,000 live births)[101]. Rates of premature birth are also higher for minority groups. Data from 2003 show that the rate of premature birth was 17.6 percent among African Americans and 13.5 percent among American Indians, whereas the rate for Whites was 11.5 percent and the rate for Asians and Pacific Islanders was 10.5 percent. For African Americans, there is also a higher percentage of low-birth-weight babies. In 2003, 13.4 percent of African American babies were born at low birth weight, compared with 6.9 percent of White babies.

The prevalence of type 2 diabetes in the African American population is nearly 70 percent higher than among Whites. American Indians and Alaska Natives have a diabetes rate more than twice that of Whites. Other health disparity populations, such as Hispanics and Asians/Pacific Islanders, also suffer disproportionately from diabetes and its complications. Hispanics are twice as likely to die from diabetes as are Whites and also have higher rates of obesity and high blood pressure[102].

The prevalence of asthma among non-Hispanic African Americans was approximately 30 percent higher than among non-Hispanic Whites and approximately double that of Hispanics[103].

---

[97] For more information, see http://www.cdc.gov/nchs/data/hus/hus06.pdf

[98] For more information, see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5419a2.htm

[99] For more information, see http://seer.cancer.gov/csr/1975_2004

[100] For more information, see http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2005report/

[101] For more information, see http://www.cdc.gov/nchs/data/nvsr/nvsr54/nvsr54_19.pdf

[102] For more information, see http://www.cdc.gov/nchs/nhis.htm; http://www.cdc.gov/nchs/products/elec_prods/subject/nhanes3.htm; http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2003.pdf; http://www.cdc.gov/mmwR/preview/mmwrhtml/00055489.htm

[103] For more information, see http://www.niaid.nih.gov/publications/minorityhealth.pdf

Disease burden associated with mental disorders varies across ethnic minority populations. Native American and Alaska Natives, for example, not only suffer disproportionately from depression but also experience a higher rate of suicide than other populations[104]. 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[105]. Differences also exist within 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[106].

Many oral and dental diseases, including early childhood caries, oral clefting, oral cancers, and some types of periodontitis are more common, more severe, and more often untreated in disadvantaged populations, such as racial and ethnic minorities, low-income families, and inner-city and rural residents[107].

Clearly, these and the many other disproportionate burdens of disease suffered by racial and ethnic minorities and other 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

In FYs 2006 and 2007, NIH funding for minority health and health disparities was $2.766 billion and $2.744 billion respectively. The table at the end of this chapter indicates some of the research areas involved in this investment (see "Estimates of Funding for Various Diseases, Conditions, and Research Areas").

Summary of NIH Activities

NIH has made a strong commitment to reduce and ultimately eliminate health disparities in the United States. 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, it is appropriate that this commitment is embodied in a wide variety of programs and initiatives, many of which address multiple elements, including population research. Although Research, Outreach, and Research Capacity are the major categories addressed in the *NIH Health Disparities Strategic Plan, Fiscal Years 2004-2008*, many NIH research projects span two or all three of those endeavors. This section will address each of the major categories, providing illustrative examples, along with discussion of several important exemplary programs and/or accomplishments that do not conform to a single category.

Research

Basic, Clinical, and Translational Research

One of the most important steps on the path to eradicating health disparities is to gain useful new knowledge regarding the causes, mechanisms, natural history, prevention, and treatment of diseases in which disparities have

---

[104] For more information, see http://www.cdc.gov/ncipc/pub-res/natam.htm

[105] Joe S, et al. *JAMA*. 2006;296:2112-23, PMID: 17077376

[106] Takeuchi DT, et al. *Am J Public Health*. 2007;97:11-12, PMID: 17138903

[107] For more information, see http://www.nidcr.nih.gov/DataStatistics/SurgeonGeneral/sgr/execsum.htm

been demonstrated. As the Nation's leader in biomedical research, NIH conducts and supports basic, clinical, and translational research designed to illuminate the relationship between disease and disparities and improve patient quality of life.

For example, sickle cell disease, caused by a genetic defect, afflicts mainly African Americans, 1 in 12 of whom carries the trait. NIH funds 10 Comprehensive Sickle Cell Centers (CSCCs), which focus on multidisciplinary programs of basic, applied, and clinical research and also provide relevant patient services in diagnosis, counseling, and education concerning sickle cell disease and related disorders. The CSCCs also support multicenter Phase II clinical trials, neuroimaging studies, and the development of a collaborative database of individuals from participating centers who are potentially eligible for inclusion in any sickle cell research study. Ten centers are funded through FY 2007, and the program will be renewed in FY 2008.

The Jackson Heart Study, a partnership of NIH and three local academic institutions, is the largest investigation of cardiovascular disease that has been undertaken in an African American population—a cohort of more than 5,000 African Americans in the Jackson, Mississippi, area. Death rates for cardiovascular disease in the United States are considerably higher among African Americans. Cardiovascular disease death rates in Mississippi are the highest in the Nation and are particularly high among African Americans. One important component of this longitudinal study is the use of new imaging techniques to assess physiological characteristics that may yield a significant additional understanding of heart disease in this minority population.

The Centers of Research Translation program translates basic research discoveries into clinical trials for diagnostic approaches and treatments. The focus of one of the current centers is on lupus, an autoimmune disease that disproportionately affects African American women as well as women of Hispanic, Asian, and Native American descent. Investigators are examining the role of different cell types in the origin and development of lupus and developing markers of disease activity and severity with the goal of identifying new targets for treatment.

Epidemiological/Population Research

NIH fosters considerable epidemiological and population research conducted mainly to identify, quantify, and characterize health disparities among populations, to test and monitor the effectiveness of potential interventions, and to monitor the health status of minority groups.

Four large-scale epidemiological studies help to demonstrate NIH activities in this sector. The Hispanic Community Health Study, launched in 2006, is the largest long-term epidemiological study of health and disease in Latin American populations living in the United States. As many as 16,000 subjects of Hispanic origin—4,000 at each of four sites—will undergo a series of physical examinations and interviews to help identify the prevalence of and risk factors for a wide variety of diseases, disorders, and conditions. They also will be followed over time to monitor the occurrence of disease. The study will seek to determine the role of cultural adaptation and disparities in the prevalence and development of disease. It also will investigate why Hispanics are experiencing increased rates of obesity and diabetes and yet have fewer deaths from heart disease than non-Hispanics, and why asthma is more common in certain Hispanic groups.

The need to understand the sources of persistent health disparities in overall longevity, cardiovascular disease, and cerebrovascular disease has led to the development of the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study. By posing fundamental questions about differences in rates and risks for pathological conditions associated with aging, the study aims to disentangle the relationship between race, socioeconomic status, and health outcomes. HANDLS will include 4,000 subjects drawn from socioeconomically diverse African American and White adults in Baltimore, Maryland. The cohort will be followed over a 20-year period to allow longitudinal assessment of aging-related variables and their potential impact on health disparities.

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. Thirty thousand individuals, about 50 percent African American and 50 percent White, are participating in REGARDS, which has already yielded important new information about disparities in stroke.

NIH is collaborating on and supporting the Collaborative Psychiatric Epidemiology Surveys, large national surveys exploring the prevalence and characteristics of mental health disorders in the United States. The National Comorbidity Survey-Replication (Harvard Medical School), the National Latino and Asian American Study (Cambridge Health Alliance/Center for Multicultural Mental Health Research), and the National Survey of American Life (Program for Research on Black Americans/University of Michigan's Institute for Social Research) will each contribute important information on disparities in the incidence of psychiatric illnesses and mental health service usage and access among racial and ethnic minorities.

Outreach

Outreach encompasses many forms of activity, with information and intervention campaigns targeted to a wide variety of audiences, including patients, health care providers, public health educators and officials, policymakers, professional and patient advocacy organizations, and community-based groups. Disseminated information may be oriented toward a particular disease (e.g., diabetes, oral cancer, stroke), a particular group (e.g., African American men, Hispanics at high risk of HIV/AIDS, women of reproductive age), or both. Along with communications, outreach initiatives also include activities such as consultations, internships, and partnerships and collaborations with various public and private organizations.

For example, NIH and CDC work together in a grassroots education campaign called Know Stroke in the Community, which enlists community leaders to become “Stroke Champions” to educate their neighbors about the signs and symptoms of stroke. The program focuses on reaching African Americans, Hispanics, and seniors (see also the section “Health Communication and Information Campaigns and Clearinghouses” in Chapter 3). Additionally, NIH collaborates with the National Coalition of Ethnic Minority Nurses Associations to increase awareness of NIH research opportunities for underserved investigators.

A wide variety of programs conduct interventions and education directly in communities in need. NIH's Oral Health Disparities Centers, which use innovative, low-cost approaches to address severe early childhood caries and oral cancer, are an excellent example of this approach. With the promising achievements of the five currently funded centers and the ongoing need to reverse severe disparities in oral health among some populations, NIH announced in May 2007 that it will fund a competing renewal of the initiative.

Many programs aim to increase health literacy among affected groups and/or to help disparity populations overcome existing barriers to access to health care. Cultural relevancy is an important factor in the success of these efforts to effectively communicate science-based medical and health information to minorities and underserved populations.

In some instances, the approach can be as straightforward—and as powerful—as communicating important information in another language. For example, *info*SIDA is a Spanish-language version of the comprehensive AIDSinfo Web site administered by NIH. Some health disparities outreach efforts are segments of wider campaigns. Others expand upon successful campaigns by incorporating culturally relevant scenarios. For example, rather than translating its “Learn the Link” public service announcement about the link between noninjection drug abuse and

HIV, NIDA created a culturally relevant public service announcement that would resonate with Hispanic audiences and released both Spanish-language and bilingual versions for English-language stations with large Hispanic audiences. The National Diabetes Education Program (NDEP) and the National Kidney Disease Education Program (NKDEP) both tailor materials for minority groups at high risk. With diabetes rates soaring within the Hispanic population, NDEP's action plan encourages Hispanics to manage the "ABCs" of diabetes—**A**1C (a test that measures 120-day blood glucose levels), **B**lood pressure, and **C**holesterol—to lower their risk for cardiovascular disease and other diabetes complications to improve their health and the health of future generations. NKDEP targets certain materials to African Americans, who are disproportionately vulnerable to kidney disease due in large measure to their elevated rates of diabetes and high blood pressure. More comprehensively, the National Network of Libraries of Medicine, with more than 5,800 full and affiliate members, is a key component of NIH'S outreach program and its efforts to reduce health disparities and improve health information literacy, particularly for underserved populations.

Enhanced access and improved care are the goals of the Patient Navigation Research Program, an initiative that provides individualized attention to cancer patients, survivors, families, and caregivers, to help them access and then chart a course through the complexities of the health care system and overcome any barriers to quality care. The Community Networks Program aims to reduce and eliminate cancer health disparities among racial and ethnic minorities. Twenty-five projects across the United States and American Samoa address cancer disparities among African Americans, American Indians, Alaska Natives, Native Hawaiians and other Pacific Islanders, Asians, Hispanics, and rural underserved populations.

Research/Outreach

Many NIH activities that address minority health and health disparities incorporate a synergistic blend of research and outreach. These projects may involve one or more outreach elements such as education, awareness, recruitment of study/clinical trial subjects, and a variety of clinical and preventive interventions, often translational in nature. Frequently, programs provide information and interventions 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. Many such programs incorporate community-based participatory research, in which scientific inquiry is conducted in partnership with the community of patients, caregivers, and other stakeholders who participate in the research.

Head Off Environmental Asthma in Louisiana (HEAL), funded in part by NIH, illustrates these concepts in its activities in post-Katrina New Orleans. Childhood asthma is on the rise in the United States, especially among minority inner-city children. Up to 24 percent of minority children living in cities like New Orleans may have asthma. The rapidly increasing rates of asthma are thought to be related in part to increases in allergies and environmental exposures, such as mold, moisture, and other allergens. Lack of access to health care may be another contributing factor. Those problems are especially prevalent in post-Katrina New Orleans, where HEAL conducts research on the effects of exposure to mold and other indoor allergens on children with asthma, as well as inherited differences in their responses. HEAL research will yield important biomedical knowledge about a growing public health problem while contributing to improved care for children with asthma in a challenging environment.

The Gila River Indian Community Longitudinal study of Pima Indians of Arizona, who have the highest prevalence of diabetes in the world, has made substantial progress in identifying genetic, physiologic, and behavioral factors that contribute to obesity and diabetes. The community has benefited from improved treatment and prevention services, leading to better blood glucose control and blood pressure among the Pima with diabetes.

The Look AHEAD (Action for Health in Diabetes) multicenter clinical trial is following 5,100 obese subjects with type 2 diabetes for 11.5 years. The study's objective is to compare the effects on cardiovascular outcomes of a long-term intensive lifestyle intervention designed to achieve and maintain weight loss, as well as a control program of diabetes education and support. The project includes considerable outreach activities to help subjects improve their health.

Low health literacy is a widespread problem, affecting more than 90 million adults in the United States, many of whom are members of disparity populations facing several other barriers to care. *Understanding and Promoting Health Literacy*, a Program Announcement by NIH and the Agency for Healthcare Research and Quality, is designed to encourage empirical research on health literacy concepts, theory, and interventions, to help accomplish the HHS *Healthy People 2010* objective of improved national health literacy by the decade's end.

Research Training

Promoting diversity in education and research is an essential component of the NIH mission to improve health through research. NIH and ICs provide several intramural and extramural programs to promote diversity in research training, increasing the breadth of representation and participation of groups that have been shown to be underrepresented, including individuals from underrepresented racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds. These programs address all career levels in the biomedical and behavioral sciences workforce and include clinical research training. The Minority Biomedical Research Support's (MBRS's) Support of Competitive Research (SCORE) Institutional Development Award program supports research projects that foster diverse faculty and student participation in biomedical research, thereby helping to create a growing and diverse cadre of scientists who are making important contributions in the health sciences. The Research Initiative for Scientific Enhancement (RISE) program develops the research potential of faculty and students. NIGMS also supports several research training programs to increase diversity in the biomedical research workforce: the Minority Access to Research Careers (MARC) Undergraduate Student Training in Academic Research (U-STAR) program, predoctoral fellowships, faculty fellowships and Visiting Scientist Fellowships, ancillary training activities, and the Post-Baccalaureate Research Education Program (PREP). The MBRS and MARC programs are institutional programs and do not use race or ethnicity as a criterion for individua ls supported by the program. Many of these programs are offered by the NIGMS's Division of Minority Opportunities in Research, which maintains a Web site that provides centralized information and an overview of programs by career stage. Other examples of extramural and intramural programs include the NIH Academy; the Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research, as mandated by Federal law (Section 487(a)(4) of the Public Health Service Act, as amended); the Undergraduate Scholarship Program (UGSP), as mandated by Federal law (Section 487D of PHS Act, as amended); and the Research Supplements to Promote Diversity in Health-Related Research (Diversity Supplements; PA 05-015).

Research Capacity

To accomplish its mission to reduce and ultimately eliminate health disparities in the United States, NIH believes that it is imperative to increase and enhance research capacity in this area in order to ensure that current and future needs are addressed. The ultimate goals are to support research, expand opportunities in training, foster career development, and increase research funding for health disparities research. A variety of projects address the need to recruit, retain, and provide career development opportunities for all scientists (particularly those from underrepresented backgrounds), as well as to expand the number of investigators pursuing health disparities

research. Such programs provide direct support to individuals and also fund expansion and infrastructure improvements at numerous institutions, including historically Black colleges and universities and others commonly referred to as minority-serving institutions.

Many ICs have existing programs that contribute to increased research capacity in the area of minority health and health disparities. NCMHD leads the Federal effort at NIH to stimulate new research and promote programs aimed at expanding the participation of underrepresented minorities in all aspects of biomedical and behavioral research. The Research Infrastructure in Minority Institutions (RIMI) research infrastructure grant program is designed to strengthen the research environment of predominantly minority-serving academic institutions through grant support to develop and/or expand existing capacities for institutional and/or individual faculty-initiated basic, biomedical, social, and/or behavioral research programs. Two NIH loan repayment programs seek to recruit and retain highly qualified health professionals who have doctorate degrees and are from health disparity populations and disadvantaged backgrounds to pursue health disparities or clinical research; they are Loan Repayment Program for Minority Health Disparities Research and the Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds[108]. Today, the NIH has 71 Health Disparities Centers of Excellence across the Nation. These Centers of Excellence, now located in 26 States, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands, support health disparities research, research training, and community involvement to identify factors that contribute to health disparities and to develop and implement new diagnostic, treatment, and prevention strategies (see Chapter 4).

The Research Centers in Minority Institutions (RCMI) Program 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." RCMI support includes funds to recruit established and promising researchers, acquire advanced instrumentation, modify laboratories for competitive research, and to fund core research facilities and other research support. The Institutional Development Award (IDeA) program fosters health-related research and increases the competitiveness of investigators at institutions in 23 states and Puerto Rico, which have historically low aggregate success rates for grant awards from NIH. The program facilitates multidisciplinary collaborations, provides workforce development, enhances research infrastructure, and supports research to reduce health disparities in minority populations within IDeA-eligible states, such as among American Indians, Alaska Natives, Hispanics, and Native Hawaiians and other Pacific Islanders. Each of these and many similar programs throughout NIH contribute to eliminating health disparities in the United States by addressing the national need to develop a diverse, strong, and culturally competent scientific workforce, and by fostering increased research activity focused on health disparities.

Conclusion

The goal of 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 and well-being of all Americans. Every IC has its own strategic plan to combat health disparities in its area of influence. Agency-wide activities are guided by the comprehensive NIH Health Disparities Strategic Plan, Fiscal Years 2004-2008, with NCMHD serving as the focal point for planning and coordinating minority health and health disparities research. NIH is also committed to broadening collaborative relationships developed through partnerships between NIH and institutions and researchers from all populations.

[108] Sec. 485 G of PHS Act, as amended; Sec. 487 E - F of PHS Act, as amended.

Health disparities arise due to a complex matrix of physical and cultural influences, and a robust, integrative, sustained approach is required to meet the profound challenges they represent. As has been seen in this chapter, that is precisely the approach being taken by NIH in its efforts to eradicate one of the Nation's most perplexing and intransigent public health problems.

Notable Examples of NIH Activity

Key for Bulleted Items:

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, and communication)
COE = Supported through a congressionally mandated **C**enter **o**f **E**xcellence program
GPRA = Concerns progress tracked under the **G**overnment **P**erformance and **R**esults **A**ct

Basic, Clinical, and Translational Research

Sildenafil for Pulmonary Hypertension in Adult Patients with Sickle Cell Disease: In 2006, NIH began a new study to evaluate a course of treatment with sildenafil in patients with sickle cell disease who have pulmonary hypertension. A randomized, double-blind, placebo-controlled, Phase II clinical trial is testing the drug's safety and efficacy in improving exercise capacity, symptoms, and measures of circulatory function. The trial involves approximately 180 patients at extramural sites and at the NIH Clinical Center. Because pulmonary hypertension occurs frequently in persons with sickle cell disease and confers a high risk of death, a positive outcome of this trial would represent an important step toward improved patient care.

- For more information, see http://www.clinicaltrials.gov/ct2/show/NCT00492531?term=sildenafil
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E/I) (NHLBI)

Comprehensive Sickle Cell Centers (CSCCs): The CSCCs were established in 1972 in response to a Presidential initiative and a Congressional mandate to support multidisciplinary research to expedite development and application of new knowledge for improved diagnosis and treatment of sickle cell disease. In addition to basic research, training, and patient services activities, the CSCCs currently support multicenter Phase II trials, neurocognitive and neuroimaging studies, development of a collaborative database, and a study on the epidemiology of priapism (painful, prolonged erection) among sickle cell patients. Ten centers were funded through FY 2007, and the program was in FY 2008.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-06-008.html
- For more information, see http://www.sicklecell-info.org/
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (NHLBI)

Jackson Heart Study: The Jackson Heart Study, a large epidemiological study of cardiovascular disease (CVD) among over 5,300 African American residents of Mississippi, has been renewed through FY 2013. The project is exploring genetic, biological, and environmental factors that influence the development and course of CVD in African Americans. It is also seeking to expand minority participation in public health and epidemiological research by providing classes and hands-on training to interested undergraduate students. Moreover, a community health education component is using data derived from the study cohort to develop and disseminate up-to-date information on reduction of risk factors, practice of healthy lifestyles, and adherence to proven risk-reducing therapies.

- For more information, see http://jhs.jsums.edu/jhsinfo/
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (**NHLBI**, NCMHD)

Centers of Research Translation (CORT): NIH launched its CORT program to unite basic and clinical research in a way that translates basic discoveries into diagnostic approaches and treatments. The first set of centers, focusing on lupus, orthopaedic trauma care, scleroderma, and a genetic form of rickets (a childhood disorder characterized by a softening and weakening of bones), began in FY 2006 and are funded through FY 2011.

- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/11_08.asp
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NIAMS)

Translational Research for the Prevention and Control of Diabetes and Obesity: NIH is supporting research projects to explore ways to bring knowledge from successful clinical research into medical practice and community settings. Studies are seeking to develop effective, sustainable, and cost-effective methods to prevent and treat type 1 and type 2 diabetes and obesity in clinical health care practice and other real-world settings. Many of these studies focus on minority populations disproportionately burdened by type 2 diabetes and obesity.

- 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)

Trans-NIH Management and Coordination of HIV/AIDS Research in Racial and Ethnic Populations: In the United States, AIDS disproportionately affects racial and ethnic minority populations. NIH response to the HIV/AIDS epidemic is a unique and complex multi-institute, multidisciplinary research program. NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection and its associated co-infections, opportunistic infections, malignancies, and other complications that are prevalent in or specific to racial and ethnic populations in the United States. This research transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every NIH IC. The Office of AIDS Research (OAR), located within the NIH Office of the Director, coordinates the scientific, budgetary, and policy elements of NIH AIDS research and has established a specific focus on the epidemic in minority communities. The Racial and Ethnic Minorities section of OAR has established the Ad Hoc Working Group on Minority Research, which includes representatives from key ICs, other HHS agencies, and non-Government experts and community representatives to assist in the development of an annual strategic plan and for collaboration and information exchange about scientific priorities and opportunities. Through its unique, trans-NIH planning, budgeting, and portfolio assessment processes, OAR ensures that research dollars are invested in the highest-priority areas of scientific opportunity, allowing NIH to

pursue a united research front against the epidemic in U.S. minority populations.

- For more information, see http://www.oar.nih.gov
- (O) (OAR)

Osteoarthritis: African Americans have a higher risk of both bilateral radiographic (x ray-defined) knee and hip osteoarthritis than Whites. Two NIH-funded studies have revealed that mechanical stress can increase the production and release of osteoarthritis-related biomarkers. The research highlights the importance, when analyzing biomarkers, of considering the type and degree of physical activity in which patients with osteoarthritis participate.

- O'Kane JW, et al. *Osteoarthritis Cartilage* 2006;14:71-6, PMID: 16188465
- Piscoya JL, et al. *Osteoarthritis Cartilage* 2005;13:1092-9, PMID: 16168680
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*
- (E) (NIAMS)

Systemic Lupus Erythematosus (Lupus): The incidence of lupus is three times higher in African American women than in White women, and it is also more common in women of Hispanic, Asian, and Native American descent. NIH-supported researchers have reported that, for most women with moderate lupus that is inactive or stable, taking estrogen—whether as oral contraception or hormone replacement therapy—appears to have no detrimental effect on disease activity. Additionally, researchers working in mice have shown that blocking the effects of two proteins, which normally recognize viruses and bacteria and activate immune cell responses against them, produced different and unexpected effects on disease severity, suggesting these proteins might be new targets for lupus treatment.

- Petri M, et al. *N Engl J Med* 2005;353:2550-8, PMID: 16354891
- Christensen SR, et al. *Immunity* 2006;25:417-28, PMID: 16973389
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2005/12_22.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/proteins_lupus.asp
- (E) (**NIAMS**, NCMHD, NCRR, NIAID, ORWH)

Vitiligo: Vitiligo is a skin disease characterized by a loss of pigment in all people who are affected. The psychological and social consequences can be particularly profound in affected people of color. A study of 133 families with vitiligo found that family members, even those who do not have vitiligo, are also predisposed to other, potentially more serious autoimmune diseases.

- Jin Y, et al. *N Engl J Med* 2007;356:1216-25, PMID: 17377159.
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/04_10.asp
- This example also appears in Chapter 2: *Autoimmune Diseases.*
- (E) (**NIAMS**, NIAID, NIDDK)

Epidemiological/Population Research

Multi-Ethnic Study of Atherosclerosis (MESA): In an ancillary study to the NHLBI-sponsored MESA, retinal disease was assessed in more than 6,000 African American, Hispanic, White, and Asian subjects in this large, population-based study of cardiovascular health. The eyes of African American and Hispanic study subjects are more likely to have signs indicative of diabetic eye disease, whereas the eyes of White and Chinese subjects are more likely to show signs of age-related macular degeneration. Other analyses demonstrate racial and/or ethnic differences in

the relative size and characteristics of the blood vessels lining the back of the eye, which are associated with various cardiovascular profiles. Future analyses will expand on these results and will consider the impact of genes, alone and in combination with differential exposure to environmental factors, such as cigarette smoke and air pollution, on retinal health.

- For more information, see http://www.mesa-nhlbi.org/default.aspx
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E/I) (**NHLBI**, NEI)

Value of early HIV Screening, Testing, and Counseling: HIV/AIDS disproportionately affects several minority groups, particularly African Americans. Although adult and adolescent African Americans make up approximately 13 percent of the population, they accounted for half of the new HIV/AIDS diagnoses in 2001-2005. This disparity is particularly striking because African Americans do not have higher rates of addiction or intravenous drug use than Whites. One contributing factor is that African Americans are often diagnosed with HIV infection at a later point in the illness, increasing their likelihood of progressing to AIDS and of transmitting the disease. As part of efforts to 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. Indeed, 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. These findings have important public health implications, recognized by CDC, 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/ResearchReports/hiv/hiv.html
- For more information, see http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm
- This example also appears in Chapter2: *Infectious Diseases and Biodefense* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIDA)

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. Recruitment to date, which has resulted in almost 2,000 subjects in the Baltimore area, will continue for 2 additional years to complete cohort recruitment of 4,000 subjects. Scientists are using mobile medical research vehicles to make possible on-site bone density and carotid artery imaging, physical examination and blood sampling, physical and cardiovascular performance, subject interviews, cognitive testing, and psychophysiological testing. HANDLS will also include studies of other variables, including: nutrition, environment and neighborhood effects, genetic make-up, family history, access to health care. Subjects 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
- (I) (NIA)

National Epidemiologic Survey on Alcohol and Related Conditions (NESARC): This nationally representative survey collected comprehensive, detailed data from approximately 40,000 individuals on alcohol consumption, use of 10 categories of drugs, and symptoms of alcohol and specific drug use disorders, as well as mood, anxiety, and personality disorders. In addition to diagnostic criteria, NESARC assessed indicators of impairment and distress due

to each disorder, as well as disorder-specific treatment and help seeking. Analysis of these data is ongoing and continues to provide valuable information such as prevalence and comorbidity of mental health and substance use disorders. In addition, because NESARC data includes a representative sample of ethnic and racial minority populations in the United States, a better assessment of the needs of specific populations can be made. One recent study using this data examined differences in the use of alcohol treatment services across the three largest ethnic groups in America. It showed Hispanics and African Americans with higher levels of problem severity were less likely to have used treatment services than Whites with problems of comparable severity, providing useful information about disparities in treatment utilization.

- Schmidt LA, et al. *Alcohol Clin Exp Res* 2007;31:48-56, PMID: 17207101
- For more information, see http://pubs.niaaa.nih.gov/publications/arh29-2/toc29-2.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E/I) (NIAAA)

A Look at Drug Abuse Trends: Local to International: Several major systems of data collection are helping to identify substance abuse trends locally, nationally, and internationally: Monitoring the Future Survey (MTF), the Community Epidemiology Work Group (CEWG), and the Border Epidemiology Work Group (BEWG). All 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 are also 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 biennially, or 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. A recently established Border Epidemiology Work Group represents a collaboration of researchers from both sides of the U.S.-Mexico border. Of special interest are drug abuse patterns and problems in geographically proximal sister cities/areas. Development of a Latin American Epidemiology Network is under way. NIH has also 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: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (NIDA)

HEALTHY: The HEALTHY multicenter clinical trial aims 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 three major risk factors for diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease risks for obesity and diabetes. In the full-scale HEALTHY trial, 42 enrolled middle schools receive the intervention, which includes changes to school food service and physical education classes, behavior change, and communications campaigns. More than 80 percent of the enrolled students are from minority populations.

- For more information, see http://www.nih.gov/news/pr/aug2006/niddk-28.htm

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (NIDDK)

Head Off Environmental Asthma in Louisiana: Nearly 20 million people, 6.5 million of them children, suffer from asthma in the United States, and minorities are disproportionately represented. NIH and others, co-fund the Head Off Environmental Asthma in Louisiana (HEAL) project to assess the impact on asthma of environmental health conditions that were caused and exacerbated by Hurricane Katrina in New Orleans children, as well as implement an intervention program to address these problems. The Project's three main goals are (1) to conduct an extensive epidemiology study to assess the nature of the environmental and psychological impacts on children in New Orleans of Hurricane Katrina and subsequent flooding; (2) to examine the genetic and environmental risk factors for asthma, including genetic susceptibility to mold toxins, and gene interactions; and (3) to design, implement, and evaluate a case management program to meet the health care needs of children with asthma in a disrupted and highly challenging environment. The project has a clear plan for informing the community of the goals, implementation, and outcome, as well as for receiving input from the community.

- For more information, see http://heal.niehs.nih.gov/
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (I) (NIEHS, NCMHD)

NIH Collaborative Psychiatric Epidemiology Surveys (CPES): Through cooperative agreements, NIH supports the National Comorbidity Survey Replication (NCS-R), the National Latino and Asian American Study (NLAAS), and the National Survey of American Life (NSAL). These studies are large, nationally representative surveys assessing the prevalence and correlates of mental health disorders. The NLAAS provides national information on the similarities and differences in mental illness and service use of Latinos and Asian Americans. The objectives of the NSAL are to investigate the nature, severity, and impairment of mental disorders among national samples of the African American and non-Hispanic White populations in the United States.

- For more information, see http://www.hcp.med.harvard.edu/ncs
- For more information, see http://www.multiculturalmentalhealth.org/nlaas.asp
- For more information, see http://www.rcgd.isr.umich.edu/prba/nsal.htm
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (NIMH)

Hispanic Community Health Study: In October 2006, NIH began the largest long-term epidemiological study of health and disease ever conducted in people of Latin American heritage living in the United States. The project, which will include about 16,000 subjects, is designed to identify factors that predispose individuals to develop heart disease, stroke, asthma, COPD, sleep disorders, dental disease, hearing loss, diabetes, kidney disease, liver disease, cognitive impairment, and other chronic conditions. Characteristics such as diet, physical activity, obesity, smoking, blood pressure, blood lipids, acculturation, socioeconomic status, psychosocial factors, occupation, health care access, environment, and use of medications and dietary supplements will be assessed.

- For more information, see http://www.nhlbi.nih.gov/new/press/06-10-12.htm
- 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, ODS)

Jackson Heart Study Advanced Imaging Component: The Jackson Heart Study is a longitudinal study of heart

disease and cardiovascular disease in about 5,000 African Americans in the Jackson, Mississippi area. Data collection for this study began in 2000. New imaging techniques that include dynamic MRI of the heart to assess cardiac function and computed tomography (CT) imaging to assess visceral abdominal fat and calcification of the aorta and coronary vessels. These imaging data can provide significant additional understanding of heart disease in this minority population. NIH is in the process of adding these valuable components to the study of heart disease. The CT studies began in spring of 2007, and the MRI studies will begin in early 2008.

- For more information, see http://www.nhlbi.nih.gov/about/jackson/index.htm
- (E) (**NIBIB**, NCMHD, NHLBI)

U.S.-Born Children of Immigrants May Have Higher Risk for Mental Disorders Than Parents: In the first studies to examine the effects of immigration and years of residence on the mental health of Caribbean Black, Latino, and Asian populations in the United States, NIH-funded researchers found that immigrants in general appear to have lower rates of mental disorders than their U.S.-born counterparts.

- For more information, see http://www.nimh.nih.gov/press/immigrant_mentalhealth.cfm
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E) (NIMH)

Retinopathy Occurs in Middle-Aged Adults Even Without Diabetes: Signs of retinopathy are common in the eyes of the elderly, particularly in those with diabetes. In the Atherosclerosis Risk in Communities (ARIC) Study, African American subjects were significantly more likely to have signs of retinopathy (13 percent) than were White subjects (5.5 percent). Among people with diabetes, 27 percent had signs of retinopathy. Unexpectedly, retinopathy signs were also observed in 4.3 percent of people who did not have frank diabetes but tended to have elevated blood pressure. Future studies will examine whether these signs of retinopathy result from high blood pressure and whether they indicate an increased risk of systemic cardiovascular disease or predict a subsequent diagnosis of diabetes.

- Wong TY et al. *Am J Ophthalmol 2007;143:970-6*, PMID: 17399675
- For more information, see http://www.cscc.unc.edu/aric
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (E/I) (**NHLBI**, NEI)

Outreach

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 material on diabetes and kidney disease, respectively. For example, the NDEP encourages people to take “small steps” to prevent type 2 diabetes. NKDEP encourages African American families to discuss kidney disease at family reunions. Both Programs tailor materials for minority groups at high risk. Information Clearinghouses also provide key health information for the public. Recent campaigns raised awareness of celiac disease and interstitial cystitis. The Weight-Control Information Network provides science-based information on topics such as obesity and nutrition.

- For more information, see http://www2.niddk.nih.gov/HealthEducation/
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*

- (E) (**NIDDK**, CDC)

National Network of Libraries of Medicine: With more than 5,800 full and affiliate members, the National Network of Libraries of Medicine is the core component of the National Library of Medicine's outreach program and its efforts to reduce health disparities and to improve health information literacy. The Network also seeks to build and improve collaborations with community-based organizations as an effective means of reaching these populations. A major new initiative is the development of a nationwide emergency plan to ensure backup health library services in the aftermath of a disaster and to establish librarians as key community resources in disaster planning and response. In 2006, new 5-year contracts were signed for eight Regional Medical Libraries in the Network.

- For more information, see www.nnlm.gov
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (I) (NLM)

Patient Navigation Research Program (PNRP): PNRP is an intervention that addresses barriers to quality standard care by providing individualized assistance to cancer patients and survivors and their families. The program's aim is to decrease the time between a cancer-related abnormal finding, definitive diagnosis, and delivery of quality standard cancer care. PNRP will focus on the four cancers with the greatest disparity in screening and follow-up care: breast, cervical, prostate, and colorectal. Nine PNRPs reach African Americans, American Indians, Asians, Hispanics/Latinos, and rural underserved populations.

- For more information, see http://crchd.cancer.gov/pnp/pnrp-index.html
- This example also appears in Chapter 2: *Cancer.*
- (E) (NCI)

SIDS Outreach in Minority Communities: Since 1994, when NIH launched its campaign to reduce the risks of sudden infant death syndrome (SIDS), rates have declined more than 50 percent. Yet the disparities in the SIDS rates that existed 13 years ago continue. Today African American infants are twice as likely to die from SIDS as White infants. To help eliminate this disparity, NIH collaborated with national African American women's organizations whose members are conducting community and neighborhood workshops to highlight important yet easy steps to help reduce the risk of SIDS. In Mississippi, where the infant mortality and SIDS rates are among the highest in the country, small stipends from NIH help community organizations conduct SIDS risk reduction workshops in rural parts of the state.

- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (NICHD)

Reducing Disparities in Stroke: NIH is actively 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 **RE**asons for **G**eographic **and R**acial **D**ifferences in **S**troke (REGARDS) Study is an observational study to explore the role of race and geographic differences on the prevalence of stroke risk factors and on stroke incidence and mortality. To date, researchers have recruited approximately 27,000 of a projected 30,000 individuals (about 50 percent African American and 50 percent White) and have already published a number of important findings on their baseline data. NIH has also established an acute stroke research and care center at the Washington Hospital Center, 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 the use of tissue plasminogen activator among minorities.

The program directly addresses GPRA Goal SRO-8.9.2: "By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities."

- 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)

Promoting Early Detection of Oral Cancer in African American Men: NIH is developing a new series of oral cancer education materials specifically for African American men, who have the highest risk of oral cancer and the lowest 5-year survival rate (only 35.6 percent) of any population in the United States. This is the first national-level effort of its kind. The first piece in the series, "Are You at Risk for Oral Cancer? What African American Men Need to Know," is now being pretested in Washington, DC; Chicago; Los Angeles; and Columbia, South Carolina. The brochure—along with other complimentary education tools, such as fact sheets, posters, and both print and audio public service announcements—will be distributed to African American community groups around the country.

- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E/I) (**NIDCR**, NCI)

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 minority, underserved, and rural kindergarten to grade 12 (K-12) students and (2) engaging and educating the general public on the 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. Moreover, SEPA is helping to bridge the educational gap and provide the next step in research and clinical pipelines for K-12 students interested in pursuing a career in biomedical science and providing professional development opportunities for teachers. Culturally appropriate projects have been developed to enhance the participation of African American, Hispanic, Alaska Native, American Indian, and Native Hawaiian communities. In FY 2007, SEPA supported 70 projects, of which 50 targeted middle- and high-school students and 20 were based in science centers and museums.

- For more information, see http://www.ncrrsepa.org/
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (NCRR)

Cancer.gov in Español: This Spanish-language version of the NCI Web site is designed to reach the Hispanic-Latino population—the fastest-growing online audience in the country—to communicate the message that cancer can be prevented and treated and to offer information on all aspects of the disease. The site is specifically tailored for Hispanics and Latinos, and pages are organized around issues of greatest concern. The site will be updated with evidence-based approaches and emerging technologies to ensure that accurate, relevant, and audience-appropriate information is provided. The site demonstrates the commitment to reducing cancer health disparities by making information readily available to underserved populations.

- For more information, see http://www.cancer.gov/espanol

- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (NCI)

Research/Outreach

Community-Based Participatory Research (CBPR) 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. This initiative began in FY 2005 with the award of 25 3-year research planning grants. 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. This phase will be followed by a competition for 5-year intervention research grants to be awarded in FY 2008 and will conclude with a 3-year research dissemination grant to be awarded in FY 2013. The current CBPR planning grantees are conducting needs assessments, focus groups, and pilot intervention studies for addressing health disparities in diabetes, cancer, cardiovascular diseases, HIV, depression, dental caries, and other diseases and conditions among health disparity populations in 20 states. In May 2007, RFA MD-07-003, "NCMHD Community-Based Participatory Research (CBPR) Initiative in Reducing and Eliminating Health Disparities," was issued for the 5-year intervention research phase. Awards for this phase will be made in FY 2008. Current CBPR pilot intervention research studies include:

- 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
- Dental caries prevention among American Indian children in North and South Dakota, Nebraska, and Iowa
- Cancer prevention among African Americans in Denver, Colorado by working with churches and faith-based organizations
- Hypertension prevention among Filipino Americans in New York City and New Jersey
- HIV/AIDS prevention among African Americans in North Carolina

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/rfa-md-07-003.html
- (E) (NCMHD)

Centers of Excellence Program: The congressionally mandated NCMHD Centers of Excellence Program[109] 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 supported 88 centers since its inception and has created hundreds of unique partnerships focused on health disparities with hospitals; tribal groups; health plans; health centers; community and faith-based organizations; civic and nonprofit health

[109] Pub. L. No. 106-525, Section 485F

organizations; and local, city, and State Governments. Of the 88 centers, 31 Exploratory Centers and 26 Comprehensive Centers are currently active. The research conducted by NCMHD Centers of Excellence and its community partners is contributing to both the scientific and lay knowledge base through numerous publications in the peer-reviewed scientific literature; press releases; television spots; other media, including Web sites 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 31 States, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. In FY 2007, new or continuing awards establishing NCMHD Centers of Excellence were made to 40 institutions. Examples of NCMHD Centers of Excellence program projects include:

- Perceived Discrimination in Healthcare Among American Indians/Alaska Natives
- Religious Outlook on Organ and Tissue Sharing: Inflammation and Asthma
- Impact of Coronary Heart Disease Risk Perception on Health Behaviors
- Physical Activity Assessment in Multi-Ethnic Women

    - (E) (NCMHD)

Research Partnerships: Fostering partnerships is a key component of the multifaceted NIH strategic approach to eliminating health disparities. The NCMHD funds a broad range of collaborations with the other NIH ICs, HHS, and other Federal agencies. Through these co-funded projects, the NCMHD magnifies its reach by leveraging the existing strengths, resources, and research potential of its key Federal research partners through an extensive array of research and training initiatives. Since its creation in 2001, NCMHD has provided more than $300 million to support several hundred research, training, community outreach, and capacity-building projects. The NCMHD will continue to build and support viable partnerships with emphasis on engaging faith-based and community-based organizations in research and outreach. Examples of research partnerships include:

- *Jackson Heart Study* (with NHLBI), a longitudinal epidemiological study of African Americans, examines genetic, biological, and environmental risk factors for the development and progression of cardiovascular disease.
- *Sister Study* (with NIEHS) is a national study that investigates environmental and genetic breast cancer risk factors in living or deceased sisters with breast cancer.
- *Hispanic Community Health Study* (with NHLBI and others) is the largest epidemiological study of health and disease in U.S. Hispanic populations.
- *Health Disparities Bench-to-Bedside Program* (with the NIH Clinical Center) fosters collaborations between basic and clinical investigators and enhanced recruitment and retention of racial and ethnic minorities in NIH clinical research.
- *Bridges to the Future Program* (with NIGMS) promotes partnerships leading to improvement in the pool of underrepresented students being trained as the next generation of scientists.
- *Tribal Epidemiology Centers Program* (with the Indian Health Service) provides epidemiological analysis, interpretation, and dissemination of information and the development and implementation of disease control and prevention programs aimed at eliminating health disparities experienced by American Indians and Alaska Natives.
- *Racial and Ethnic Approaches to Community Health* (REACH 2010) (with CDC) is a national program for limited large-scale population surveys and surveillance systems to monitor the health status of minority populations.

    - (E) (NCMHD)

Look AHEAD (Action for Health in Diabetes): This multi-center NIH-led clinical trial is examining the health effects

of an intensive lifestyle intervention designed to achieve and maintain weight loss over the long term, through decreased caloric intake and increased physical activity. The impact of the intervention on the incidence of major cardiovascular events will be evaluated in 5,100 overweight or obese subjects with type 2 diabetes. Look AHEAD is one of four trials that collectively address GPRA Goal SRO-6.2.

- The Look AHEAD Research Group. *Diabetes Care* 2007;30:1374-83, PMID: 17363746
- For more information, see http://tinyurl.com/2xaypk
- 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 Goal)

Community Networks Program (CNP): This program aims to reduce and eliminate cancer disparities among racial minorities through community-based research, education, and training. The goals of the program are to significantly improve access to and the utilization of beneficial cancer interventions in communities with cancer disparities. A total of 25 projects across the United States and in American Samoa were launched in May 2005 to address cancer disparities among African Americans, American Indians/Alaska Natives, Hawaiian Natives and other Pacific Islanders, Asians, Hispanics/Latinos, and rural underserved populations. Ten grantees work in local areas, 10 in regional areas, and 5 in national programs. Visit: http://crchd.cancer.gov/cnp/overview.html.

- This example also appears in Chapter 2: *Cancer*.
- (E) (NCI)

Collaborative Community-Based Research: NIH is focusing on strategies and best practices for conducting collaborative community-based clinical and translational research, particularly in minority communities and other medically underserved communities where health disparities persist. The Institutional Development Award (IDeA) and Research Centers in Minority Institutions (RCMI) programs are encouraging efforts to build and strengthen partnerships among Government agencies and academic and private-sector organizations that are also working to improve community health outcomes. Translational, community-based research funded in several IDeA states and RCMI-supported Centers, 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 FY 2007 NIH conducted two workshops to gather specific recommendations from the community that will help shape future initiatives to enhance clinical and translational research in minority and other medically underserved communities (www.esi-bethesda.com/ncrrworkshops/Fostering/index.aspx). Workshop subjects included other HHS-agencies, such as AHRQ, CDC, the Indian Health Service, and HRSA.

- For more information, see www.ncrr.nih.gov/research_infrastructure
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NCRR)

Health Partnership Program and Community Health Center: The Health Partnership Program (HPP) is a community-based, collaborative research program between NIH and Washington, DC, area representatives. Through research with underrepresented patients affected by arthritis and other rheumatic diseases, the HPP studies health disparities and their causes and provides direction for improving the health status and outcomes of

affected minority communities. Its Community Health Center (CHC) is the platform for HPP's research, education, and training activities. The Washington, DC, Center provides the community with access to specialized care and health information and NIH researchers with access to patients most affected by rheumatic diseases. Recently, NIH published "Exploring Perceptions About the Ethics of Clinical Research in an Urban Community."

- Grady C et al. *Am J Public Health* 2006;96:1996-2001, PMID: 17018826
- For more information, see http://www.niams.nih.gov/About_Us/Mission_and_Purpose/Community_Outreach/Health_Partnership/default.asp
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (I) (NIAMS)

Oral Health Disparities Centers Initiative: In May 2007, NIH announced plans to fund a competing renewal of the Oral Health Disparities Centers Initiative due to the promising achievements of currently funded centers and the magnitude of the need for scientific advancement to eliminate disparities. Despite the remarkable improvement in the Nation's oral health over the years, not all Americans have benefited equally. Oral, dental, and craniofacial conditions remain among the most common health problems for low-income, disadvantaged, and institutionalized Americans. Unfortunately, there is no easy, one-size-fits-all solution. Much remains to be learned about the complex array of cultural, economic, genetic, and other contributory factors to these disparities and how best to overcome them. The five currently supported Centers have devised innovative, low-cost approaches to address severe early childhood caries, oral cancer, poor diet, and malocclusion.

- For more information, see http://grants1.nih.gov/grants/guide/rfa-files/RFA-DE-08-008.html
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIDCR)

The Gila River Indian Community Longitudinal Study: The NIH's Phoenix Epidemiology and Clinical Research Branch studies type 2 diabetes as it occurs among Pima Indians of Arizona, who have the highest prevalence of diabetes in the world. Working closely with Pima volunteers, the Branch has made substantial progress in identifying genetic, physiologic, and behavioral factors that lead to obesity and diabetes. The Branch also has facilitated improved treatment and prevention services in this community, leading to improved blood glucose control and blood pressure in Pima with diabetes. One important result is that the rate of kidney failure due to diabetes in Pima 45 years of age and older has declined since 1990.

- For more information, see http://intramural.niddk.nih.gov/research/labbranch.asp?Org_ID=503
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies.*
- (I) (NIDDK)

Rural and Frontier Mental Health: In 2006 and 2007, NIH held several technical assistance workshops in frontier communities, such as Anchorage, Alaska, in order to improve the competitiveness of research grant applications submitted by rural mental health researchers. NIH also convened workshops in Mississippi to enable community mental health workers to cope with the aftereffects of hurricanes.

- (E) (NIMH)

Know Stroke in the Community Educational Campaign: In 2004, NIH entered a first-time partnership with the Centers for Disease Control and Prevention (CDC) to launch a new grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders called

"Stroke Champions" who worked to educate communities about the signs and symptoms of stroke. The program focuses on reaching African Americans, Hispanics and seniors in communities that have the health care systems in place to treat stroke. In 2005-2006, the program had been implemented in 11 cities, educating 168 Stroke Champions who have conducted more than 600 community events.

- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses* and Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NINDS)

***Info*SIDA:** NIH introduced *info*SIDA, a Spanish-language version of the AIDS*info* Web site, an HHS-established site that offers the latest federally approved information on HIV/AIDS clinical research, treatment and prevention, and medical practice guidelines. *Info*SIDA features a customized home page and a search engine that locates Spanish-language resources within AIDS*info*. The steering group spans NIH (OAR, NIAID, and NLM), FDA, HRSA, the Center for Medicare and Medicaid Services, and CDC.

- For more information, see http://aidsinfo.nih.gov/infoSIDA
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (I) (NLM)

Minority Health: NIH works in a number of ways to share health information and develop the capacity of minority-serving educational institutions to access and use health information. NLM-sponsored programs focused on historically Black colleges and universities, the National Medical Association and their more than 25,000 physicians and associated patients of African descent, health information networks for refugees, special Web sites with health information for specific populations (Asian Americans, American Indians, peoples of the Arctic), and information fellowships for representatives from American Indian tribes, Native Alaskan villages, and the Native Hawaiian community.

- Dutcher G, et al, *J Med Libr Assoc* 2007;95:330-6, PMID: 17641769
- 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)

Community-Based Participatory Research (CBPR): CBPR is scientific inquiry conducted in communities and in partnership with researchers. Persons affected by the health condition or issue under study, or other key stakeholders in the community's health, fully participate in each phase of the work. This input offers CBPR the potential to generate better-informed hypotheses, develop more effective interventions, and enhance the translation of research results into practice. The Program Announcement "Community Participation in Research" supports CBPR on health promotion, disease prevention, and health disparities. CBPR is also the theme of the annual NIH Research on Social Work Interventions and Health Summer Institute (July 2007).

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-283.html
- For more information, see http://obssr.od.nih.gov/summerinstitute2007/index.html
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (**OBSSR**, AHRQ, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINR, NIOSH)

Effect of Racial and Ethnic Discrimination/Bias on Health Care Delivery: A recent report from the Institute of Medicine on unequal treatment, as well as several other recent reviews, show that racial/ethnic minorities less frequently receive appropriate care, which has an adverse impact on their health outcomes, including higher

recurrence rates, morbidity, and mortality. This Program Announcement supports research directed at developing methodology and defining the specific ways in which institutional or personal bias influence the health status, health outcomes, and utilization of health services among racial/ethnic minority patients. The Funding Opportunity Announcement also supports the development of interventions designed to reduce racial/ethnic bias or perceptions of racial/ethnic bias in the health care setting.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-206.html
- (E) (**OBSSR**, NCI, NHLBI, NIBIB, NIDA, NIDDK)

Understanding and Promoting Health Literacy: The HHS Healthy People 2010 initiative established a national health objective to improve health literacy by the decade's end. Although many diseases and conditions can be prevented or controlled, too often people with the greatest health burdens have few fact-finding skills, the least access to health information, and least effective communication with health care providers. This 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.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-020.html
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses.*
- (E) (**OBSSR**, AHRQ, NCI, NHLBI, NIA, NIBIB, NICHD, NIDCD, NIDCR, NIEHS, NIMH, NINR, NLM)

Understanding and Reducing Health Disparities: Behavioral and Social Sciences Research Contributions: This October 2006 conference highlighted three broad areas of action influencing health disparities: policy, prevention, and health care. These themes are the focus of "Behavioral and Social Science Research on Understanding and Reducing Health Disparities." These Program Announcements invite applications for basic research on the behavioral, social, and biomedical pathways giving rise to disparities in health as well as applied research on the development, testing, and delivery of interventions to reduce disparities in these three action areas. They encourage a multilevel, analytic framework (i.e., ranging from individuals to societies) and systems analytic approaches. They include research relevant to a wide range of population groups (e.g., variation by socioeconomic status, race/ethnicity, and rural-urban locality) residing in the United States. Consideration is given to multiple public health issues and their interactions (e.g., multiple morbidities rather than single illnesses) and to risk factors or causal processes common to various health conditions (e.g., smoking, diet, exercise, access to health care).

- For more information, see http://obssr.od.nih.gov/HealthDisparities/index.html
- 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
- (E) (**OBSSR**, CDC, NCCAM, NCI, NCMHD, NEI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS, NINR, NLM)

Minority Participation in Clinical Trials: NIH researchers recently reported several trust-enhancing strategies identified through a process of community engagement that may help scientists successfully recruit clinical research subjects in medically underserved populations. Open communication, ensuring confidentiality, and being attentive to the patient's rights before, during, and after the clinical trial are key.

- Grady C et al.*Am J Public Health* 2006;96:1996-2001, PMID: 17018826
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/trial_participation.asp

- (O) (NIAMS, CC)

Culturally Sensitive Educational Program Promotes HIV Prevention Among Latino Adolescents: In the first randomized, controlled trial of a culturally tailored HIV risk reduction program for Hispanic adolescents, NIH-supported investigators reported long-term success in reducing risk behaviors. HIV and AIDS disproportionately affect Hispanic adolescents; the incidence of AIDS for adult and adolescent Hispanics in 2001 is more than three times higher than among their non-Hispanic White counterparts. Subjects in the study were randomly assigned to one of two interventions: a general health promotion program or the HIV education/prevention program called "íCuidate!" ("Take Care of Yourself"). Both programs presented Hispanic cultural values as an important context that supports positive health behaviors. The study found that the adolescents who received the HIV prevention program reported a lower frequency of sexual intercourse, fewer sexual partners, and an increased use of condoms during intercourse for up to 12 months after completing the program. Results also suggested that it is beneficial to provide education on both abstinence and safe sex practices.

- Villarruel AM, et al. *Arch Pediatr Adolesc Med* 2006;160:772-7, PMID: 16894074
- For more information, see http://www.nih.gov/news/pr/aug2006/ninr-07.htm
- (E) (NINR)

Research Training

Minority Biomedical Research Support/Research Initiative for Scientific Enhancement MBRS/RISE):[110] MBRS was created in response to a legislative mandate to "increase the numbers of underrepresented minority faculty, investigators and students engaged in biomedical and behavioral research, and to broaden the opportunities for underrepresented minority faculty and students for participation in biomedical and behavioral research." Hence, the objective of the MBRS program is to support research projects that foster diverse faculty and student participation in biomedical research, thereby helping to create a growing and diverse cadre of scientists who are making important contributions in the health sciences. To accomplish these goals, RISE provides support for faculty and student development activities, which can include on- or off-campus workshops, specialty courses, travel to scientific meetings, and research experiences at on- or off-campus laboratories. Support is also available for evaluation activities. RISE also offers some support for institutional development, which includes limited funds for the renovation or remodeling of existing facilities to provide space for an investigator to carry out developmental activities, limited equipment purchases, and the development of research courses.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-05-127.html
- (E) (NIGMS)

Minority Access to Research Careers (MARC) Undergraduate Student Training in Academic Research (U-STAR): MARC supports special research training opportunities for students and faculty. MARC programs also enable grantee institutions to develop and strengthen their biomedical research training capabilities. As a result, these schools are able to interest students in, and prepare them for, the pursuit of doctoral study and biomedical research careers. MARC training grants and fellowships include U-STAR institutional grants, predoctoral fellowships, faculty predoctoral and senior fellowships, and a visiting scientist program.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-337.html

[110] Section 301(a)(3) of the PHS Act, as amended [42 U.S.C. 241 (a)(3)].

- (E) (NIGMS)

Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research:[111] The goal of this program is to provide biomedical and behavioral research and research training programs that will result in the recruitment of women and individuals from disadvantaged backgrounds (including racial and ethnic minorities) in an effort to ensure that diverse pools of highly trained scientists will be available in appropriate research areas to carry out the Nation's biomedical, behavioral, health services, and clinical research agenda. The means used is to improve the diversity of the health-related research workforce by supporting the training of predoctoral students from groups that have been shown to be underrepresented. Such candidates include individuals from underrepresented racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds. These fellowships will enhance the diversity of the biomedical, behavioral, health services, and clinical research labor force in the United States by providing opportunities for academic institutions to identify and recruit students from diverse population groups to seek graduate degrees in health-related research and apply for this fellowship.

- For more information, see http://grants1.nih.gov/grants/guide/pa-files/PA-07-106.html
- (E) (**OD/OER**, NCI, NCCAM, NCRR, NEI, NHLBI, NHGRI, NIA, NIAID, NIAMS, NIBIB, NICHD, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NIGMS, NIMH, NINDS, NINR, ODS)

NIH Research Supplements to Promote Diversity in Health-Related Research: These research supplements, formerly known as Research Supplements for Underrepresented Minorities and Research Supplements for Individuals with Disabilities, have broad eligibility criteria that include consideration of a larger number of backgrounds that could disadvantage individuals. The primary aim of this supplement is to promote diversity in the biomedical, behavioral, and clinical and social sciences research workforce through the recruitment and retention of (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 recognizes a unique and compelling need to promote diversity in the biomedical, behavioral, clinical, and social sciences research workforce. 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.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-05-015.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-05-015.html
- (E) (NCMHD) All NIH ICs participate in this program.

Minority Institutional Research Training Program: The purpose of this Kirschstein-NRSA training program is to support training of graduate and health professional students and individuals in postdoctoral training at minority schools that have the potential to develop meritorious training programs in cardiovascular, pulmonary, hematologic, and sleep disorders.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-04-027.html
- For more information, see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-043.html

[111] Section 487(a)(4) of PHS Act, as amended.

- (E) (NHLBI)

Minority Institutions' Drug Abuse Research Development Program (MIDARP): This program aims to support minority institutions wishing to develop their capacity to conduct drug abuse research. Two programs funded under this PA have focused on Hispanic issues in drug abuse. New MIDARP programs have been established at Universidad del Caribe, Hampton University, and Florida International University. MIDARP is based on a program developed approximately 20 years ago. The current program was developed according to the definition of "minority institutions" that is commonly used by NIH and other HHS agencies, for example, historic designations such as "historically Black colleges and universities" and student enrollment data. In addition, since this is a capacity development program, consideration is given to the applicant organization's history of sponsored research in drug abuse and addiction. The program will be reviewed to ensure that it furthers NIDA's science and scientific workforce needs and NIH expectations and policies regarding equitable access to research opportunities for all population groups.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-05-069.html
- (E) (NIDA)

NINR Mentored Research Scientist Development Award for Underrepresented or Disadvantaged Investigators: NINR recognizes a unique and compelling need to promote diversity in the biomedical, behavioral, clinical, and social sciences research workforce, specifically in nursing research investigators. This award program is one approach to increasing the diversity of nurse investigators and enhancing the research capabilities of historically underrepresented or disadvantaged scientists in nursing research by providing additional research career development opportunities with financial support. These awards train scientists in a mentored setting in the development of research programs, in preparation for becoming independent investigators. NINR also recognizes the lack of diversity of qualified nurse scientists in research settings. This award program seeks to address this problem by enhancing the research capabilities of underrepresented or disadvantaged nurse investigators so that these individuals may establish research laboratories and research programs in nursing science. There is abundant evidence that the research, biomedical, and health enterprise will directly benefit from this broader inclusion. The focus of activities for the awardees in this program is mentored research experience to enhance the candidate's career or to gain expertise in a research area new to the candidate.

- For more information, see http://grants1.nih.gov/grants/guide/pa-files/PAR-05-135.html
- (E) (NINR)

Minority Health and Health Disparities International Research Training (MHIRT) Program: In 2006, NIH provided funding for the Minority Health and Health Disparities International Research Training (MHIRT) Program, which allowed 24 academic institutions to implement international training opportunities in health disparities research for more than 150 undergraduate and graduate students. The MHIRT Program contributes to the elimination of health disparities in the United States by developing researchers who better understand health disparities issues from various international perspectives. Many MHIRT subjects are engaged in research that investigates genetic, socioeconomic, behavioral, psychosocial, and fundamental determinants of health disparities. MHIRT trainees are placed worldwide to conduct research and complete their training. The current MHIRT program expires in 2008, and a new MHIRT RFA that will build on the success of the existing program is being developed. In 2006, the majority of MHIRT research projects were focused on biomedical issues related to improving minority health and eliminating health disparities. African American and Latino (Hispanic) undergraduate and graduate students constitute the largest racial and ethnic groups participating in MHIRT training programs.

- (E) (NCMHD)

Loan Repayment Programs: To effectively promote a diverse and strong scientific workforce, it is necessary to expand and create transitioning and financial aid programs that help alleviate barriers that often discourage many students from pursuing a research career. The NIH Loan Repayment Programs address this national need by encouraging the recruitment and retention of minority and other scientists in the fields of biomedical, clinical, behavioral, and health services research. Specifically, the Loan Repayment Program for Health Disparities Research (HDR-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 focus of the Extramural Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds (ECR-LRP) is 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, the NIH will work to establish links between the LRPs (HDR-LRP and ECR-LRP) and the NIH research priorities.

- (E) (NCMHD, OER)

NIH Academy: The NIH Academy provides opportunities for recent college graduates to spend a year engaged in biomedical investigation at the NIH campus. The mission of the Academy is to enhance research dedicated to the elimination of domestic health disparities through the development of a diverse cadre of biomedical researchers. Participants in this program work side by side with some of the leading scientists in the world in an environment devoted exclusively to biomedical research. Seminars and workshops round out the training experience.

- For more information, see http://www.training.nih.gov/student/pre-irta/previewacademy.asp
- (I) (OD/OIR)

Undergraduate Scholarship Program (UGSP): The NIH Undergraduate Scholarship Program (UGSP) for students from disadvantaged backgrounds was authorized by statute in 1994 and established in 1996. UGSP participants, as mandated under section 487D of the Public Health Service Act, receive up to $20,000 in scholarship support to defray educational expenses. Scholarship recipients are required to be employees at the NIH IRP for 10 weeks during the summer for each year of scholarship support and to have 1 year of research employment for each year of scholarship support after their graduation. The 1-year service payback can be deferred until the receipt of a terminal degree (Ph.D., M.D., M.D/Ph.D., etc). The aim of the program is to provide students from disadvantaged backgrounds the opportunity to be trained and hired as employees in the NIH Intramural Research Program. To date, 102 students have been awarded scholarships.

- For more information, see http://www.ugsp.nih.gov/home.asp?m=00
- (I) (OD/OIR)

Biomedical Research Training Program for Underrepresented Minorities: This program has provided minority undergraduate, graduate, and health professional students majoring in the life sciences with the opportunity to receive training in the NHLBI intramural laboratories. This program has been renamed and re-announced as the NHLBI Biomedical Research Training Programs for Individuals from Underrepresented Groups (BRTPUG) to reflect broadened eligibility criteria for the recruitment and participation of diverse individuals in research and research training programs.

- For more information, see http://www.nhlbi.nih.gov/funding/training/redbook/brtpug.htm

- (E/I) NHLBI

Diversity Inventory: This work in progress is an effort to catalogue existing programs, described in the NIH Health Disparities Strategic Plan, that aim to create a culturally competent workforce by expanding opportunities for research training, career development, and institutional research capacity and infrastructure. This searchable database will be made available online as a comprehensive source of information for potential applicants or other constituents who are interested in NIH programs that are designed to promote diversity in the biomedical research workforce. This inventory will serve as a baseline for the diversity workgroup that was formed to identify and address gaps and needs in the current diversity recruitment practices.

- (O) (**NIGMS, NCMHD**, OER, OWH)

Research Capacity

The Minority Institution/Cancer Center Partnership (MI/CCP): The MI/CCP program, initiated in April 2000 as a collaboration between NCI and NCMHD, is focused on developing comprehensive partnerships between NCI-designated Cancer Centers and institutions where students who are underrepresented in the biomedical sciences make up a significant proportion of the enrollments as designated by the U.S. Department of Education as Minority-Serving Institutions (MSI). The aims of these partnerships are (1) to provide cancer research training and education to qualified underrepresented students and investigators to strengthen diversity in the cancer research professions and to encourage recruitment of the most talented researchers to pursue careers in research in cancer and cancer health disparities; (2) to improve the quality of the outreach, training, and educational environment for cancer research at the partnering institutions; (3) to improve the ability to recruit subjects from diverse backgrounds into clinical research protocols; and (4) to strengthen the National Cancer Program by broadening the perspective of the cancer research community in setting cancer research priorities and improving the Nation's capacity to address and eliminate health disparities.

- This example also appears in Chapter 2: *Cancer.*
- (E) (NCI)

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 provided for the creation of this unique program, which makes significant investments in the education and training of underrepresented minority and socioeconomically disadvantaged individuals. The Research Endowment Program is an important priority and represents one of the NCMHD cornerstone programs. NCMHD-endowed institutions are using endowment funds to enhance research capacity and infrastructure for research and training, which include 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: The Research Infrastructure in Minority

Institutions Program (RIMI) program was originally created by the NIH National Center for Research Resources (NCRR) and the NIH Office of Research on Minority Health (ORMH), the predecessor to the NCMHD. The RIMI research infrastructure grant program is designed to strengthen the research environment of predominantly minority-serving academic institutions through grant support to develop and/or expand existing capacities for institutional and/or individual faculty initiated basic, biomedical, social, and/or behavioral research programs. The program is flexible and allows institutions to pursue, for example, research efforts that address health disparities among racial and ethnic minorities and the medically underserved, including those who reside in the Southwest Border States, rural communities, Appalachia Region, Mississippi Delta, Frontier States and urban centers of the United States. Further, the RIMI Program helps non-doctoral degree institutions to develop and enhance their capacity and competitiveness to conduct biomedical or behavioral research and develop their research infrastructure, primarily through collaborations with research-intensive universities.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-MD-07-002.html
- (E) (NCMHD)

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 that historically have not received significant levels of competitive research funding from NIH. The IDeA program supports multidisciplinary centers and State-wide 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 Lariat, a pilot program that has enabled connectivity in six states (Alaska, Hawaii, Idaho, Montana, Nevada, and Wyoming). IDeANet ultimately will enable all institutions in the IDeA program, as well as subjects in NIH's Research Centers in Minority Institutions program, to engage in national and international collaborations.

- For more information, see http://www.ncrr.nih.gov/research_infrastructure/institutional_development_award
- For more information, see IDeA program evaluation GPRA goal 8.4
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NCRR) (GPRA Goal)

Research Centers in Minority Institutions (RCMI): The Research Centers in Minority Institutions (RCMI) Program 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.” RCMI support includes funds to recruit established and promising researchers, acquire advanced instrumentation, modify laboratories for competitive research, and to fund core research facilities and other research support. Because many investigators at RCMI institutions study diseases that disproportionately affect minorities, NCRR support serves the dual purpose of bringing more minority scientists into mainstream research and enhancing studies of minority health. The next step in increasing the research capacity of the RCMIs is to link each of them together.

- For more information, see www.ncrr.nih.gov/research%5Finfrastructure/research%5Fcenters%5Fin%5Fminority%5Finstitutions/
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NCRR, NCMHD, NHLBI, NIA, NIAID, NIAMS, NICHD, NIDA, NIDDK, NIMH)

- (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 by mentoring minorities for careers in research on minority health among older adults, 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. An independent evaluation of the success of the RCMAR program is in progress.

- For more information, see http://www.rcmar.ucla.edu
- (E) (NIA)

Combating Health Disparities: NIH conducts research designed to identify racial and ethnic disparities in the causes and consequences of alcohol use disorders and to develop treatment and prevention strategies to ameliorate them. NIH contributes to all HHS and White House initiatives designed to address health disparities by (1) increasing access to and participation in HHS programs, (2) increasing the capacity of minority institutions to conduct research, and (3) promoting health data collection on racial and ethnic minority populations. For example, between 1998 and 2003, NIH increased the capacity of eight minority or minority-serving institutions to conduct alcohol research, using several cooperative agreement mechanisms. Two of these projects have ongoing activity.

- (E) (NIAAA)

Collaboration with National Coalition of Ethnic Minority Nurse Associations (NCEMNA): NIH conducts outreach activities focused on health disparities research through its relationship with the National Coalition of Ethnic Minority Nurse Associations (NCEMNA). Comprising 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)

NIH Strategic Plans Pertaining to Minority Health and Health Disparities Research

NIH-Wide Strategic Plan

- *NIH Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities, Fiscal Years 2002-2006*
  CC, CSR, FIC, NCCAM, NCI, **NCMHD**, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM, OAR, OBSSR, OIR, ORD, ORWH

Note: Every IC has a Strategic Plan on Health Disparities. These plans are contained with the NIH plan.

- *NIH Health Disparities Strategic Plan, Fiscal Years 2004-2008*
  (To be published; approved by the National Advisory Council on Minority Health and Health Disparities, but awaiting formal clearance)

National Institute on 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 Draft Strategic Plan*

Summary of Research Activities by Disease Categories

Estimates of Funding for Various Diseases, Conditions, and Research Areas

The table below provides insight into NIH research funding on the topics addressed in this chapter. The table is adapted from the most recent[112] version of NIH's Estimates of Funding for Various Diseases, Conditions, and Research Areas (http://www.nih.gov/news/fundingresearchareas.htm). That publicly available source table displays information that NIH routinely collects on agency-wide funding in areas of special interest. For each area in which NIH collects data on agency-wide funding, the table below indicates whether some of the funding pertains to the topics in this chapter.

Important Notes:

- The FY 2006 and FY 2007 funding levels are based on actual grants, contracts, intramural research, and other mechanisms of support.
- The figures provided are not allocated or set aside for these areas. Rather, the funding level results from myriad individual decisions.
- Funding included in one area may also be included in other areas; for example, Clinical Research includes Clinical Trials, and Fragile X Syndrome, Genetics, and Intellectual Disability each overlap to some extent, as do Topical Microbicides, HIV/AIDS, and Prevention. Because of this overlap, adding the funding of various areas will yield a false sum.
- 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.

Research/Disease Area	Dollars in Millions		Topics						
	FY 2006 Actual	FY 2007 Actual	Cancer	Neuroscience and Disorders of the Nervous System	Infectious Diseases and Biodefense	Autoimmune Diseases	Chronic Diseases and Organ Systems[113],	Life Stages, Human Development, and Rehabilitation	Minority Health and Health Disparities

[112] February 22, 2007

[113] 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.

Acute Respiratory Distress Syndrome	$74	$48			X				
Agent Orange & Dioxin	17	18		X					
Aging	2,431	2,462	X	X	X		X	X	X
Alcoholism	511	521	X	X	X		X	X	X
Allergic Rhinitis (Hay Fever)	4	5				X			
ALS	44	39		X					
Alzheimer's Disease	643	645		X				X	
American Indians/Alaska Natives	155	141	X	X	X				X
Anorexia	15	12		X			X	X	
Anthrax	150	105			X				
Antimicrobial Resistance	221	269			X				
Aphasia	15	14		X					
Arctic	17	19			X	X			
Arthritis	355	339		X	X	X	X	X	X
Assistive Technology	182	184		X				X	
Asthma	283	294				X	X		X
Ataxia Telangiectasia	9	11		X					
Atherosclerosis	337	347		X	X		X		
Attention Deficit Disorder (ADD)	116	107		X				X	
Autism	108	127		X				X	
Autoimmune Disease	598	587		X		X			X

Basic Behavioral and Social Science	1,062	1,104	X	X	X	X	X	X	X
Batten Disease	8	8		X					
Behavioral and Social Science	3,001	3,060	X	X	X	X	X	X	X
Biodefense	1,766	1,735		X	X				
Bioengineering	1,546	1,469	X	X	X	X	X	X	
Biotechnology	9,974	9,814	X	X	X	X	X	X	X
Brain Cancer	178	193	X	X					
Brain Disorders	4,732	4,670		X	X	X			
Breast Cancer	718	707	X					X	X
Cancer	5,575	5,643	X	X	X	X		X	X
Cardiovascular	2,349	2,370	X	X			X	X	X
Cerebral Palsy	18	16		X				X	
Cervical Cancer	97	96	X						X
Charcot-Marie-Tooth Disease	7	7		X					
Child Abuse and Neglect Research	38	38		X				X	
Childhood Leukemia	53	55	X					X	
Chronic Fatigue Syndrome	5	4		X		X	X		
Chronic Liver Disease and Cirrhosis	408	379	X		X		X		
Chronic Obstructive Pulmonary Disease	67	91					X		
Climate Change	50	47	X		X				

Clinical Research	8,785	9,116	X	X	X	X	X	X	X
Clinical Trials	2,767	2,949	X	X	X	X	X	X	X
Colorectal Cancer	269	282	X						X
Complementary and Alternative Medicine	301	299	X	X	X		X		X
Conditions Affecting Unborn Children	103	110		X	X			X	
Contraception/Reproduction	335	314						X	
Cooley's Anemia	42	34					X		
Cost-Effectiveness Research	143	155	X	X	X				X
Crohn's Disease	64	69				X	X		
Cystic Fibrosis	85	82			X	X	X		
Dental/Oral and Craniofacial Disease	413	417	X	X	X		X	X	X
Depression	335	345		X			X	X	
Diabetes	1,038	1,037		X		X	X	X	X
Diagnostic Radiology	712	694	X	X					
Diethylstilbestrol	8	6	X						
Digestive Diseases	1,252	1,234	X	X	X	X	X		
Digestive Diseases (Gallbladder)	7	6					X		
Digestive Diseases (Peptic Ulcer)	17	23			X	X	X		X
Down Syndrome	14	16		X				X	
Drug Abuse (NIDA only)	990	1,001	X	X	X		X	X	X

Duchenne/Becker Muscular Dystrophy	18	23		X					
Dystonia	19	16		X					
Emerging Infectious Diseases	1,857	1,816	X		X				
Emphysema	17	21	X				X		
Endometriosis	12	12	X				X	X	
Epilepsy	103	105		X					
Estrogen	153	164	X	X				X	
Eye Disease and Disorders of Vision	705	714		X			X		
Facioscapulohumeral Muscular Dystrophy	2	4		X					
Fetal Alcohol Syndrome	29	34		X				X	X
Fibroid Tumors (Uterine)	15	14	X				X	X	
Fibromyalgia	9	9		X			X		
Food Safety	316	278			X				
Fragile X Syndrome	20	27	X	X				X	
Frontotemporal Dementia	33	31		X				X	
Gene Therapy	356	325	X	X	X	X	X		
Gene Therapy Clinical Trials	32	31	X	X	X	X	X		
Genetic Testing	417	395	X				X	X	
Genetics	4,878	4,878	X	X	X	X	X	X	X
Global Warming Climate Change	58	56			X				

Health Disparities	2,766	2,744	X	X	X	X	X	X	X
Health Effects of Climate Change	157	164	X		X				
Health Services	929	1,023	X	X	X	X	X	X	X
Heart Disease	2,087	2,126					X	X	X
Heart Disease: Coronary Heart Disease	398	382					X	X	X
Hematology	1,114	1,128	X		X	X	X		
Hepatitis	177	174	X		X		X		
Hepatitis A	3	2			X				
Hepatitis B	36	42	X		X		X		X
Hepatitis C	122	108	X		X		X		
HIV/AIDS[114]	2,902	2,906	X	X	X			X	X
Hodgkin's Disease	21	17	X						
HPV and/or Cervical Cancer Vaccines	14	20	X		X			X	
Human Fetal Tissue	23	19	X	X	X	X			
Human Genome	1,065	1,099	X	X			X		
Huntington's Disease	48	53		X					
Hyperbaric Oxygen	2	2		X					
Hypertension	395	390		X			X	X	X
Immunization	1,438	1,342	X	X	X			X	X

[114] 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.

Infant Mortality/Low Birth Weight	478	464		X	X			X	X
Infectious Diseases	3,132	3,059	X	X	X				X
Infertility	40	51						X	
Inflammatory Bowel Disease	72	80	X			X	X		
Influenza	207	271			X				
Injury (total) Accidents/Adverse Effects	355	403		X				X	X
Injury: Childhood Injuries	28	27						X	
Injury: Trauma (Head and Spine)	233	219		X				X	
Injury: Traumatic Brain Injury	85	82		X				X	
Injury: Unintentional Childhood Injury	25	21		X				X	
Interstitial Cystitis	25	23					X		
Kidney Disease	434	450	X	X	X		X		X
Lead Poisoning	15	15		X				X	
Liver Cancer	88	90	X						X
Liver Disease	450	423			X		X		
Lung	978	1,013	X				X		
Lung Cancer	266	249	X						
Lupus	97	84		X		X			
Lyme Disease	24	22		X	X				
Lymphoma	170	158	X	X	X	X			

Macular Degeneration	60	70		X			X	X	
Malaria	98	104			X				
Malaria Vaccine	35	36			X				
Mental Health	1,824	1,853		X			X	X	X
Intellectual Disability	188	204		X				X	
Methamphetamine	45	45		X			X		X
Mind and Body	136	133	X	X					
Minority Health	2,423	2,407	X	X	X	X	X	X	X
Mucopolysaccharidoses	10	10	X	X			X	X	
Multiple Sclerosis	110	98		X		X			
Muscular Dystrophy	40	47		X					
Myasthenia Gravis	9	6		X		X			
Myotonic Dystrophy	7	8		X					
Nanotechnology	192	215	X	X	X				
Networking Information Technology R&D	423	507	X				X		
Neurodegenerative	1,217	1,166		X					
Neurofibromatosis	16	13	X	X					
Neuropathy	54	59	X	X			X		
Neurosciences	4,830	4,809	X	X	X	X	X	X	X
Nutrition	1,039	1,075	X	X	X		X	X	X
Obesity	594	661	X	X			X	X	X
Organ Transplantation	363	358	X			X	X		

Orphan Drug	1,255	1,158	X	X	X	X			
Osteogenesis Imperfecta	5	5					X		
Osteoporosis	169	164					X	X	
Otitis Media	17	15			X		X		
Ovarian Cancer	102	103	X						
Paget's Disease	6	4					X		
Pain Conditions, Chronic	220	224	X	X			X		
Parkinson's Disease	208	187		X					
Pediatric	3,161	3,173	X	X	X	X	X	X	X
Pediatric AIDS	276	262	X	X	X			X	
Pediatric Research Initiative	141	171		X	X			X	
Pelvic Inflammatory Disease	4	3	X		X			X	
Perinatal: Birth, Preterm (Low Birth Weight)	374	351		X	X			X	
Perinatal: Neonatal Respiratory Distress Syndrome	8	9						X	
Perinatal Period, Conditions Originating in Perinatal Period	407	387		X				X	
Pick's Disease	1	1		X				X	
Pneumonia	145	132			X				
Pneumonia and Influenza	351	405			X				
Polycystic Kidney Disease	32	36	X				X		
Prevention	6,815	6,729	X	X	X	X	X	X	X

Prostate Cancer	348	345	X						X
Psoriasis	8	10				X	X		
Regenerative Medicine	614	575	X	X	X	X	X	X	
Rehabilitation	324	344	X	X				X	
Rett's Syndrome	5	6		X				X	
Reye's Syndrome	1	1						X	
Rural Health	202	208	X	X	X				X
Schizophrenia	364	358		X				X	
Scleroderma	11	12				X	X		
Septicemia	49	49			X				
Sexually Transmitted Diseases/Herpes	264	288	X	X	X		X	X	X
Sickle Cell Disease	91	94		X			X		
Sleep Disorders	199	190		X					
Smallpox	149	122			X				
Smoking and Health	517	534	X	X			X	X	X
Spina Bifida	11	9		X				X	
Spinal Cord Injury	66	64		X				X	
Spinal Muscular Atrophy	15	11		X					
Stem Cell Research	643	657	X	X	X	X	X	X	
Stem Cell Research: Human Embryonic	38	42		X	X	X	X	X	
Stem Cell Research: Non-Human Embryonic	110	106	X	X	X	X	X	X	

Stem Cell Research: Human Non-Embryonic	206	203	X	X	X	X	X	X	
Stem Cell Research: Non-Human Non-Embryonic	289	306	X	X	X	X	X	X	
Stem Cell Research Involving Umbilical Cord Blood / Placenta	19	22	X	X	X	X	X	X	
Stem Cell Research Involving Umbilical Cord Blood/Placenta: Human	16	19	X	X	X	X	X	X	
Stem Cell Research Involving Umbilical Cord Blood/Placenta: Non-Human	4	2	X	X	X	X	X	X	
Stroke	342	340		X				X	X
Substance Abuse	1,490	1,523	X	X	X		X	X	X
Sudden Infant Death Syndrome	77	81		X				X	X
Suicide	32	43		X				X	
Teenage Pregnancy	21	16						X	
Temporomandibular Muscle/Joint Disorder	17	15		X			X		
Tobacco	515	536	X	X			X	X	
Topical Microbicides	88	99			X			X	
Tourette Syndrome	13	11		X					
Transmissible Spongiform Encephalopathy	35	43		X	X				
Transplantation	551	534	X	X		X	X		
Tuberculosis	150	166			X				
Tuberculosis Vaccine	22	17			X				

Tuberous Sclerosis	9	12		X			X		
Urologic Diseases	536	526	X		X		X		
Uterine Cancer	28	22	X						
Vaccine Related	1,449	1,358	X	X	X			X	
Vaccine Related (AIDS)	593	597	X		X				
Vector-Borne Diseases	464	424			X				
Violence Research	113	106							X
West Nile Virus	85	69			X				
Women's Health	3,498	3,470	X	X	X	X	X	X	X