Summary of Research Activities by Key Approach and Resource

Epidemiological and Longitudinal Studies

In the midst of a devastating cholera outbreak in 1854, John Snow systematically mapped the distribution of deaths in the Soho neighborhood of London and pinpointed water from the now-famous Broad Street pump as the source of the disease. In addition to helping curb future outbreaks by advancing the notion that cholera is transmitted through contaminated water, Snow's efforts helped lay the foundation for modern epidemiological studies, which collect data and test hypotheses relative to a vast range of factors that affect diseases—from genetic variability to socioeconomic status—with the ultimate goal of improving public health.

Introduction

Epidemiological studies examine the causes of health and disease in human populations using a broad range of approaches. Persons or groups can be followed over time in longitudinal studies, or a snapshot of information can be collected at a single point in time. Studies can be done retrospectively, examining outcomes that have already occurred and factors that may have contributed to health or disease, or they can be done prospectively by beginning to monitor a population of interest before a particular disease-related outcome occurs. Some epidemiological studies, such as randomized controlled clinical trials, are experiments that actively test an intervention; others, however, are observational in nature, collecting information about and comparing groups—called cohorts—made up of individuals who share a characteristic of interest (e.g., tobacco use, age, educational status).

The varied approaches to epidemiological research can be employed to answer a broad range of questions, such as:

- "What genetic and environmental factors interact to cause cancer?"
- "What environmental or behavioral factors have led to increased rates of obesity?"
- "How well does vaccination protect elderly people from influenza?"
- "Do patterns of adolescent drug use vary by geographic region?"

In order to address these questions, epidemiological research draws on expertise from a number of disciplines, including, but not limited to, epidemiology, social and behavioral sciences such as economics and demography, genetics, and public health. Although some epidemiological studies may be adequately addressed within a single discipline, collaboration among scientists with a variety of expertise is necessary to unravel the multifarious factors that contribute to a complex disease such as cancer or diabetes.

Epidemiological research—particularly the large prospective studies with longitudinal followup that are usually the most robust and informative—is time-consuming and expensive, but NIH investment in this type of research over the past half-century continues to yield invaluable results. For example, two generations of offspring born to the original subjects in the Framingham Heart Study, which was initiated in 1948 and identified high blood pressure, smoking, and other now well-known risk factors for cardiovascular disease, are now being followed to identify hereditary factors that contribute to cardiovascular disease. Moreover, repositories of data and biospecimens collected years ago in long-running epidemiological and longitudinal studies are allowing researchers to answer the research questions of today. For example, the NIH Genes, Environment, and Health Initiative is using DNA samples collected from persons who participated in past studies to systematically identify disease-related genes and gene variants. The combination of genetic and longitudinal data should help elucidate the complex gene-environment interactions that contribute to disease.

NIH is leveraging its past investments as well as its position as one of the foremost research hubs in the world to spur the next generation of truly "big science." Although technological advances are contributing to this effort, its success is even more deeply rooted in the growing number of scientists working together in a truly interdisciplinary fashion. Such a collaborative approach permits the integration of diverse data from a variety of sources to improve understanding of (a) the factors that converge to cause disease and (b) the interventions that may reduce disease risk. Equally important, this culture of cooperation is characterized by a willingness to make results publicly available in a timely manner for the benefit of the entire research enterprise.

Beyond interdisciplinary collaboration, however, NIH also recognizes the great potential of a systems approach that integrates genetics, biology, and the social sciences, as well as multilevel studies that illuminate the mechanisms linking features of societies and communities to individual behaviors and health outcomes, often on a global level. This approach often requires an understanding of economic trends and their relationships to both acute and chronic diseases, and it demands explicit consideration of the environment in which health and disease are being studied. It recognizes that factors such as public health policy and neighborhood design may be just as important as genetic variation and individual behavior, and that addressing any of these factors in isolation will result in an inadequate understanding of health and disease. One example of a systems approach to studying disease is the International Epidemiologic Databases to Evaluate AIDS (IeDEA) consortium, which is working to harmonize HIV/AIDS data from a number of sources worldwide to gain a better understanding of HIV/AIDS pathogenesis as well as the efficacy of treatment and prevention strategies within different settings and populations.

Building on its past investment, NIH currently supports numerous epidemiological and longitudinal studies to increase understanding of diseases ranging from cancer to Alzheimer's disease to influenza. Through interdisciplinary efforts and integration of data from a variety of disciplines, NIH is helping to usher in an era of personalized medicine in which the genetic, biological, and behavioral risk factors of an individual are considered within the context of the sociocultural and physical environment. The following section provides an overview of NIH-supported epidemiological and longitudinal studies, followed by "notable examples" of NIH work in this field across different disease areas. Detailed information on clinical trials, one type of experimental epidemiological study, can be found in the section on Clinical and Translational Research in Chapter 3.

Summary of NIH Activities

The NIH mission encompasses a broad range of activities, from the pursuit of fundamental knowledge about the nature and behavior of living systems to the application of that knowledge to extend healthy life and reduce the burdens of illness and disability. As part of this continuum from basic to applied research, epidemiological and longitudinal studies are critical for the translation of research findings to real-world application at the population level. In addition to testing hypotheses generated through basic, translational, and clinical research, these types of studies often result in the formulation of new or modified hypotheses, spurring new laboratory and clinical studies. Thus, epidemiological and longitudinal studies are essential for linking bench to bedside to population and help ensure that public investment in research delivers tangible value by providing an empirical perspective on the accrual and application of scientific knowledge. Numerous prior and ongoing NIH studies have yielded results with meaningful implications for the health of the population. This progress has been due to a variety of factors, including a longstanding and continuous investment in epidemiological and longitudinal research, a deeply entrenched culture of cooperation, and a commitment to gaining a comprehensive understanding of health and disease.

Investments in the Past Continue to Pay Off

NIH has been investing in epidemiological and longitudinal studies for more than 50 years. The infrastructure created and the data collected from these studies continue to advance understanding of disease and health in new and exciting ways. Prolonged followup also has enormously increased the value of these studies, and their existence helps form the foundation for extraordinary opportunities in biomedical research today. Below are

highlights of select NIH research activities that illustrate how findings from long-term population-based studies have elucidated different facets of important public health issues.

Results of large, national longitudinal studies have helped guide medical recommendations for specific populations, substantially improving their health outcomes. For example, in 1991, NIH launched the Women's Health Initiative (WHI), a national longitudinal study that included nearly 162,000 women of many racial and ethnic backgrounds—the largest and most comprehensive study of women to date. Over the next 15 years, WHI conducted clinical trials and observational studies to identify strategies for preventing heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. One of the most important discoveries of the original WHI studies was that estrogen plus progestin hormone therapy increases risk of breast cancer and may also increase risk of coronary heart disease, stroke, and pulmonary embolism[1]. This evidence led to a precipitous drop in use of hormone replacement therapy by postmenopausal women, which is thought to have contributed to the 6.7 percent decline in breast cancer incidence observed in the following year[2]. In addition to pursuing the primary study objectives of WHI, NIH encourages investigators to take advantage of the specimens and data accumulated through WHI. To date, nearly 100 ancillary studies have been funded to research myriad issues that affect older women, from domestic violence to periodontal disease. Many of these studies are carrying earlier WHI results back to the laboratory in order to explain and build upon population-level observations. One group is surveying over 1,000 proteins in specimens collected from WHI subjects with the goal of identifying a small group of proteins that will predict both risk of disease and response to hormone therapy.

Long-term longitudinal studies also can uncover health trends related to people's social and cultural behaviors, and thus suggest new health interventions. For instance, a recent analysis of social network data collected on three generations of Framingham Heart Study subjects revealed that individuals are significantly more likely to become obese if they have a friend, sibling, or spouse who becomes obese. Interestingly, the strongest association was found between friends, not siblings, suggesting that social relationships play an even more important role in obesity than genetic background. Furthermore, the effect was not observed between neighbors who were not friends, indicating that social relationships are more important than geographic or neighborhood factors[3]. The observation that obesity—commonly attributed to genetic and individual behavioral factors—can also spread through social ties has implications for public health interventions and suggests the possibility of harnessing social networks to spread positive health behaviors.

Long-term population studies also have provided insight into intergenerational influences on health and behavior. For example, NIH facilitated extensive research on linkages between parental factors and child development by building on the U.S. Department of Labor National Longitudinal Survey of Youth —a longitudinal study designed to further understanding of how young Americans move into productive roles in the economy. In 1979, the U.S. Department of Labor began collecting health, income, and educational attainment information on a cohort of 14- to 22-year-olds. In 1986, NIH expanded the study and began amassing extensive information on children born to women of the 1979 cohort on a biennial basis; these children now range in age from 5 years to 20-something. The resulting intergenerational database combines cognitive, social, and physical information about the children with longitudinal information on family background, education, employment history, and economic well-being. Studies on children of the 1979 cohort have spawned over 1,000 publications on health and other outcomes, from the effects of family income on children's health to the effects of public policy on the investment of fathers in their children.

Longitudinal studies also can be used to inform the decisions of policymakers and assess both short- and long-term effects of policies on health or health-related behaviors. In 1975, NIH launched Monitoring the Future (MTF), a

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[1] Rossouw JE, et al. *JAMA* 2002;288:321-33, PMID: 12117397

[2] Ravdin PM, et al. *N Engl J Med* 2007;356:1670-4, PMID: 17442911

[3] Christakis NA, Fowler JH. *N Engl J Med* 2007;357:370-9, PMID: 17652652

study that tracks the beliefs, attitudes, and behaviors of adolescents and young adults. MTF surveys approximately 50,000 students in grades 8, 10, and 12 each year. Among other things, MTF gathers information on alcohol and other drug use, and its findings have been used by the Office of National Drug Control Policy to monitor progress toward national health goals. Survey results from 2007 show a 24 percent decline among the three grades combined in recent abuse (i.e., during the past month) of "any illicit drug" between 2001 and 2007. Also, during this period, marijuana abuse has decreased roughly 25 percent, and teen cigarette use has declined by a third to be the lowest point in the survey's history. The use of ecstasy has declined by more than half, and methamphetamine use has plummeted by more than 60 percent since 2001[4]. This translates to 860,000 fewer youth using illicit drugs, a testament to the impact of targeted drug abuse prevention efforts, which, by depicting emerging trends, such surveys help to inform.

Culture of Cooperation

Bridging the gap between research and application requires the contributions of numerous scientists with diverse expertise. Recognizing this, NIH fosters a culture of cooperation that has yielded consortia of scientists enthusiastic about working together in interdisciplinary teams and willing to make research results immediately and freely available for the benefit of the whole research enterprise. This emerging "big science" paradigm provides support for interdisciplinary epidemiological and longitudinal studies and also promotes the creation of resources and tools that will help the broader scientific community benefit from and build upon these studies.

NIH supports several studies that bring together expertise from multiple fields to more effectively address research questions and/or simultaneously address multiple research questions. For example, the National Longitudinal Study of Adolescent Health (Add Health) was initiated in 1994 as a joint effort of 18 NIH Institutes and Federal offices to examine how families, peers, schools, and neighborhoods influence the health-related behaviors of adolescents in grades 7 through 12. A new wave of interviews with the original Add Health cohort, now ages 24-32, will include collection of genetic data and biological markers of disease processes, in addition to 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. Working together, these diverse teams will address a broad range of research questions that collectively will yield a deeper understanding of the factors influencing the health of young people.

Other multidisciplinary endeavors at NIH have engendered collective analyses, which extend the power of these studies. As an example, the Magnetic Resonance Imaging (MRI) Study of Normal Brain Development receives contributions from several NIH Institutes and Centers, including NICHD, NIDA, NIMH, and NINDS. Researchers with expertise in child development, neuropsychology, neurology, and imaging work together to increase understanding of normal brain development. This longitudinal effort involves coordination of six Pediatric Study Centers distributed across the country, all of which use cutting-edge technology to monitor brain development in approximately 500 children from 7 days to 18 years of age. Importantly, the Centers have developed and adopted a uniform approach to collecting these images to ensure that their data can be collectively analyzed, extending the power and benefit of the study[5]. Data collected through the study are being used to build the Nation's first normative database of MRI images and accompanying clinical and behavioral data, all of which are being made available to the scientific community. This knowledge will be valuable for future laboratory and clinical studies examining the underlying causes of childhood disorders such as mental retardation, developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases.

The MRI database is only one of the many tools NIH has created to facilitate research community access to

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[4] Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. (December 11, 2007), Overall, illicit drug use by American teens continues gradual decline in 2007 University of Michigan News Service: Ann Arbor, MI. [Online].http://www.monitoringthefuture.org/

[5] Evans AC, et al. *Neuroimage* 2006;30:184-202, PMID: 16376577

emerging scientific information. These resources are particularly relevant for genomic studies. Building on recent knowledge gained through the Human Genome Project and the International HapMap Project, NIH has launched a series of consortia that combine multiple cohorts to create powerful, large-scale studies. One of these consortia, the Cancer Genetic Markers of Susceptibility (CGEMS) study, is performing genome-wide scans to identify genetic variants associated with risk for developing cancer of the breast, prostate, and colon. The Pancreatic Cancer Cohort Consortium (PanScan) is conducting an analogous scan for pancreatic cancer, and scans are under way for lung, bladder, and other cancers as well. All of the data collected through these studies will be freely available through caBIG (the Cancer Bioinformatics Grid), a bioinformatics tool being developed for the explicit purpose of transforming cancer research into a more collaborative, efficient, and effective endeavor. CGEMS researchers recently identified a common genetic variant on chromosome 8 that strongly predicts prostate cancer risk; interestingly, genetic variants in this same region also have been associated with breast and colorectal cancers[6]. These discoveries, made through population-based epidemiological studies, are already spawning new laboratory research, allowing scientists to learn more about the molecular basis of prostate and other cancers.

The NIH investment in genome-wide analyses extends well beyond cancer. The Database of Genotype and Phenotype (dbGaP) was initiated in December 2006 as a platform to archive and distribute data generated by the increasing number of studies exploring the association between specific genes and disease-related traits. dbGaP already contains data from several studies, including the Age-Related Eye Diseases Study, a prospective study of the clinical course of age-related macular degeneration and cataracts, and the Parkinsonism Study, which collected genetic information on neurologically normal and Parkinson's disease patients. This growing repository of freely available genomic data and other similar resources illustrate a staunch commitment to data-sharing that should help generate new hypotheses and spur discoveries that will eventually be translated into effective therapies.

A Comprehensive Understanding of Disease

NIH recognizes that efficient translation of scientific knowledge to population-level application requires a systems approach that integrates genetics, biology, and the social sciences, and also includes multilevel studies that illuminate the mechanisms linking features of societies and communities to individual behaviors and health outcomes. Performing these studies in diverse contexts, from the community to the global level, contributes to a more comprehensive understanding of health and disease. NIH supports a number of studies in the United States and worldwide aimed at uncovering how these diverse elements interact to influence patterns of disease with the goal of identifying new and effective approaches for prevention and treatment.

Numerous NIH-supported studies examine how genes, biology, behavior, and environment interact to influence disease risk. For example, the Jackson Heart Study, a prospective epidemiological study of cardiovascular disease among African Americans in the Jackson, Mississippi, metropolitan area, is assessing genetic and other risk factors that underlie cardiovascular disease. The study also is considering how sociocultural factors, such as racism, discrimination, and coping strategies, affect disease in African Americans. In another example, the National Children's Study will track more than 100,000 children from across the United States from the prenatal period through age 21 to examine factors ranging from natural and man-made environment to biological, genetic, social, and cultural influences. Researchers will analyze how these elements interact with each other to influence health and disease in children throughout development. Plans also are under way for the NIH-wide Genes, Environment, and Health Initiative, which will use genomics, proteomics, and metabolomics to assess how genetic variance and environmental exposures influence disease.

In addition to pursuing multifactorial explanations for disease risk, NIH is examining how diverse factors converge to influence an individual's response to interventions. In 2002, the NIH Diabetes Prevention Program revealed that individuals at high risk of type 2 diabetes could substantially lower disease occurrence through intensive lifestyle intervention. Extensive followup of the same cohort through the Diabetes Prevention Program Outcomes Study also resulted in the identification of a genetic variant that predisposes people to type 2 diabetes. Importantly,

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[6] Yeager M, et al. *Nat Genet* 2007;39:645-9, PMID: 17401363

researchers found that people with the high-risk genetic variant benefited as much or more from intensive lifestyle intervention as did those without the variant. These types of studies are becoming increasingly important as personalized medicine becomes a tangible reality. Multilevel studies will lay the groundwork for the informed selection of preventive or therapeutic interventions according to genetic, biological, behavioral, and environmental factors.

NIH also uses longitudinal and epidemiological studies to gather information on global patterns of infectious diseases. These efforts not only will advance understanding of the causes of these diseases, but also should contribute to the development of interventions to lessen disease burden in the United States and worldwide. One illustration of this is the Multinational Influenza Seasonal Mortality Study, an NIH-led collaborative that is analyzing national and global epidemiological patterns associated with influenza virus circulation. 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 better understand the global circulation patterns of influenza and their impact on populations. To this end, 20 countries have contributed data on mortality, virus surveillance, genomics, and influenza control strategies. A more comprehensive understanding of influenza epidemiology worldwide will result in the development of better vaccines as well as other types of strategies to avoid future influenza pandemics.

A global perspective is also being acquired through IeDEA (the International Epidemiological Databases to Evaluate AIDS). This regional collaborative of centers on five continents is focused on the harmonization and integration of data in order to pursue population-level research questions about HIV/AIDS that cannot be addressed in single cohorts. Topics of research will include 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.

Conclusions

Epidemiological and longitudinal studies are essential to NIH efforts in bridging the results of basic, translational, and clinical studies to applications in the general population. In addition to testing hypotheses at the population level, observations gathered through these studies help optimize existing interventions and stimulate novel laboratory and clinical research. Many NIH epidemiological and longitudinal studies have had substantial influence on public health. This success is due to a number of factors, including investment in long-term studies, promotion of a culture of cooperation, and pursuit of a comprehensive view of disease. The studies presented here represent only a fraction of NIH efforts in this area. Although still not comprehensive, additional notable examples of NIH-supported epidemiological and longitudinal studies, as well as further information about the activities mentioned above, are found in the following section.

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

Investments in the Past Continue to Pay Off

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 (FHS), 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 over 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 to integrate the wealth of information collected over the years in the FHS 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 FHS 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://www.nhlbi.nih.gov/new/press/06-02-06.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E) (**NHLBI**, NLM)

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 results of 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 over 160,000 subjects. Investigators will use stored blood, DNA, and other biological samples and 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E) (NHLBI)

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 their twenties to their nineties 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/blsanew.htm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (I) (NIA)

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 www.niams.nih.gov/News_and_Events/Advisory_Council_Minutes/2006/sum01_06.asp (Section VII - Study of Osteoporotic Fractures)
- 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 2: *Chronic Diseases and Organ Systems.*

- (E) (**NIAMS**, NIA)

Population Research: Given the Nation's increasing diversity and changing demographics, it is critical to understand how trends in such areas as immigration, fertility, marriage patterns, and family formation affect the well-being of children and families. NIH research in these areas allows policymakers and program planners to better address public health needs. For instance:

- The Fragile Families and Child Well-Being Study follows children born to unmarried parents to assess how economic resources, father involvement, and parenting practices affect children's development.

- The New Immigrant Survey follows the first nationally representative sample of legal immigrants to the United States, providing accurate data on legal immigrants' employment, lifestyles, health, and schooling before and after entering the country.

- 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. The study also follows children born to female subjects 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 2: *Life Stages, Human Development, and Rehabilitation*.
  - (E) (**NICHD**, NCI, NCMHD, NIA, NIAAA, NIAID, NIDA, NIDCD, NINR, OAR, OBSSR, ORWH)

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 towards 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 multi-city 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 2: *Minority Health and Health Disparities*.
  - (E) (NIDA)

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 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 2: *Minority Health and Health Disparities.*
- (I) (NIDDK)

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 2: *Neuroscience and Disorders of the Nervous System*
- (E) (**NIDA**, NICHD) (GPRA Goal)

The Carolina Lupus Study: Since 1997, NIH supported the Carolina Lupus Study, the first population-based epidemiologic study to examine the influence of hormonal and occupational exposures, in addition to genetic factors affecting immune function and metabolism, on systemic lupus erythematosus (SLE). SLE 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 reasons unknown. The study included 265 patients and 355 people without lupus living in 60 counties in North and South Carolina. The results for analysis of occupational exposure to silica dust in relation to risk for SLE 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 SLE 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/cls/index.cfm
- This example also appears in Chapter 2: *Autoimmune Diseases*.
- (I) (NIEHS)

Culture of Cooperation

Health Care Delivery Consortia to Facilitate Discovery and Improve Quality of Cancer: 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 over 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, for example, CRN research documenting specific gaps in implementing effective tobacco cessation services among clinicians, reasons for late diagnosis of breast and cervical cancer, more rapid uptake in the use of aromatase inhibitors in comparison to 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 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 premenopausal and postmenopausal women, and identified that although biopsy rates are twice as high in the United States in comparison to the United Kingdom, cancer detection rates are very similar in the two countries.

- In an effort to address 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, the Cancer Care and Outcomes Research Surveillance Consortium (CanCORS) was established. It 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 2: *Cancer*, Chapter 3: *Clinical and Translational Research*, and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
    - (I) (NCI)

Database of Genotype and Phenotype (dbGaP): Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics, and other scientific data, NIH established dbGaP to house this growing body of information, particularly the results of genome-wide association studies (GWAS), which examine genetic data of subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2007, dbGaP included results from more than a dozen GWAS, including genetic analyses added to the landmark Framingham Heart Study and trials conducted under the Genetic Association Information Network. dbGaP is to become the central repository for many NIH-funded GWAS in order to provide for rapid and widespread distribution of such data to researchers and accelerate the advance of personalized medicine.

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

NIH Collaborative Psychiatric Epidemiology Surveys (CPES): Through cooperative agreements, NIH supports the National Co-morbidity 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 2: *Minority Health and Health Disparities*.
- (E) (NIMH)

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/extramural consortia by creating strategic partnerships to accelerate knowledge about the genetic and environmental components of cancer induction and progression. Using 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 in order 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://cgems.cancer.gov/index.asp
- For more information, see http://epi.grants.cancer.gov/PanScan/
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Genomics*.
- (E/I) (NCI)

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, chronic obstructive pulmonary disease, 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 2: *Minority Health and Health*

Disparities.

- (E) (**NHLBI**, NCMHD, NIDCD, NIDCR, NIDDK, NINDS, ODS)

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.

- Dec. 2002 - RFA AA-03-008: "Research Partnership Awards for Rapid Response to College Drinking Problems." Five U01 (cooperative agreement) 5-year grants were awarded.
- June 2003 - PAR-03-133: "Rapid Response to College Drinking Problems." Fifteen 3-year grants were awarded.
    - 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)
    - 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: *Chronic Diseases and Organ Systems*, Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*, and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIAAA)

Polycystic Kidney Disease (PKD): The Consortium for Radiologic Imaging Studies of PKD (CRISP) showed that magnetic resonance imaging could accurately track structural changes in the kidneys in 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 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIDDK)

Health and Retirement Study (HRS): The HRS is the leading source of combined data on health and financial circumstances of Americans older than age 50 and 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 physical and mental health of older Americans, 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/
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (NIA)

Magnetic Resonance Imaging (MRI) Study of Normal Brain Development: Understanding healthy brain development is essential to finding the causes of many childhood disorders, including those related to mental retardation, developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases. NIH is creating the Nation's first database of MRI measurements and analytical tools, and clinical and behavioral data to understand normal brain development in approximately 500 children from across the Nation. This large-scale longitudinal study uses several state-of-the-art brain-imaging technologies. The data will be disseminated as a Web-based, user-friendly resource to the scientific community.

- For more information, see http://www.bic.mni.mcgill.ca/nihpd/info/index.html
- Evans AC, et al. *Neuroimage* 2006;30:184-202, PMID: 16376577
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Neuroscience and Disorders of the Nervous Systems*
- (E/I) (**NICHD**, NIDA, NIMH, NINDS)

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. 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 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/addhealt
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NICHD, NCI, NCMHD, NIA, NIAAA, NIAID, NIDA, NIDCD, NINR, OAR, OBSSR, ORWH)

Study of Normal Brain Development: The NIH Intramural Research Program is conducting studies to explore brain development in healthy children and adolescents using magnetic resonance imaging. 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 2: *Neuroscience and Disorders of the Nervous System*
- (I) (NIMH)

A Comprehensive Understanding of Disease

National Health and Nutrition Examination Survey (NHANES): CDC uses rigorous surveys such as NHANES to collect health information and disease burden statistics representative of the entire U.S. population. Surveys also

provide insight on health-seeking behaviors, as well as quality of life experiences and priorities. NIH and CDC collaborate to generate stable national estimates of vision impairment. A recent analysis of vision data indicated that 11 million of the estimated 14 million Americans with vision impairment could have their vision improved to normal levels if they had appropriate refractive correction (e.g., glasses or contact lens), including 9 percent of all young adults ages 12-19.

- For more information, see http://www.cdc.gov/nchs/nhanes.htm
- For more information, see http://www.cdc.gov/nchs/nhis.htm
- (E) (NEI)

Ocular Epidemiology Panel Report: The broad aim of National Eye Institute (NEI)-sponsored epidemiology research is to reduce the burden of visual impairment through research into the causes, diagnosis, prevention, treatment, and rehabilitation of the most prevalent blinding diseases. The ability to apply genetic and molecular tools in the context of populations, in connection with behavioral, environmental, and social factors, has transformed the potential contribution of epidemiology to the goal of controlling the major blinding diseases. NEI recently convened an expert panel to assess the unique needs and opportunities in ocular epidemiology that result from these new tools and to make recommendations for their application in future research. The panel's recommendations are contained in its report *Epidemiological Research: From Populations through Interventions to Translation.*

- For more information, see http://www.nei.nih.gov/funding/nprp.asp
- (E/I) (NEI)

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. 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/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 2: *Minority Health and Health Disparities*.
- (E/I) (**NHLBI**, NEI)

Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD): The Chronic Renal Insufficiency Cohort (CRIC) study is investigating the relationship between CKD and cardiovascular disease. With approximately 3,000 subjects, this is the largest cohort study of CKD undertaken to date. The Chronic Kidney Disease in Children Study (C-KiD) is a cohort study of 540 children. It aims to identify novel and traditional kidney disease risk factors for the progression of CKD, and to characterize the impact of a decline in kidney function on neurodevelopment, cognitive abilities, and behavior. The U.S. Renal Data System is a national data system that collects, analyzes, and distributes information about CKD and ESRD in the United States.

- For more information see http://tinyurl.com/39nk3x
- For more information, see http://www.statepi.jhsph.edu/ckid/
- For more information, see http://www.usrds.org/
- (E) (**NIDDK**, NICHD)

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 over 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 2: *Chronic Diseases and Organ Systems.*
- (E) (NIDDK, NICHD)

Diabetes Prevention Program Outcomes Study (DPPOS): The landmark NIH Diabetes Prevention Program clinical trial showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk. The DPPOS is a long-term followup study of the 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, as 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) while 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (**NIDDK**, CDC, IHS, NCMHD, NEI, NHLBI, NIA, NICHD, ORWH)

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 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 2: *Minority Health and Health Disparities.*
- (E/I) (**NIAAA**, NIDA)

Boston Area Community Health Study (BACH) Survey: Interstitial cystitis/painful bladder syndrome (IC/PBS) is a urologic condition whose prevalence is uncertain and which remains difficult to diagnose and treat. The Boston Area Community Health (BACH) Survey is a population-based study of urologic conditions, including IC/PBS, in over 5,500 adults in Boston. Results emerging from BACH about IC/PBS prevalence by demographic group, the role of

comorbid conditions, and the impact of IC/PBS on quality of life are providing a clearer picture of the IC/PBS burden in the population and will inform research efforts to reverse this burden.

- Clemens JQ, et al. *J Urol* 2007;177:1390-4, PMID: 17382739
- For more information, see http://tinyurl.com/35llmz
- For more information, see http://tinyurl.com/363842
- (E) (NIDDK)

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 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 2: *Infectious Diseases and Biodefense*.
- (O) (FIC)

Screening Infants for Congenital CMV Infection: "By 2013, develop and evaluate the efficacy of neonatal screening for congenital cytomegalovirus (CMV) infection to permit identification of infants who will develop CMV-induced hearing loss in the first years of life." Approximately 1 percent of newborns, or about 40,000 infants each year, are born infected with CMV. As much as 20 to 30 percent of childhood hearing loss is caused by CMV, the most common virus that is passed from a mother to her unborn child. However, 90 percent of CMV-infected children show no symptoms at birth. Due to the compelling but limited data on congenital CMV infection and hearing loss in infants, NIH funded a research contract to the University of Alabama School of Medicine, Birmingham (UAB). The contract funds UAB to lead a multicenter longitudinal study entitled "CMV and Hearing Multicenter Screening" (CHIMES) Study, on the role of congenital CMV in the development of hearing loss in children. A major focus of this research is identifying asymptomatic children and following their progress to determine whether hearing loss develops. The CHIMES study is one of the largest studies of its kind with approximately 100,000 children to be screened at birth for CMV infection. Those who test positive for CMV will undergo followup diagnostic hearing testing to determine the onset, severity, and progression of hearing loss. NIH-supported scientists are combining screening newborns for CMV infection with newborn hearing screening to improve our ability to detect and predict hearing loss in children.

- Fowler KB, Boppana SB. *J Clin Virol* 2006;35:226-31, PMID: 16386462
- (E) (NIDCD) (GPRA Goal)

International Training and Research Program in Population and Health: This program supports U.S. universities that provide training to scientists from developing countries in population studies or reproductive biology. Objectives of this program include enhancing population research programs and international collaborative studies on (a) reproductive processes and contraceptive development and (b) demographic processes, including aging, mortality, morbidity, fertility, migration, and linkages between health and economic development; strengthening the ability of scientists from developing nations to contribute to global population research efforts and advance knowledge in support of population policies appropriate for their home countries; and developing and strengthening centers of research excellence in population-related sciences in developing countries.

- For more information, see http://www.fic.nih.gov/programs/training_grants/itrph/index.htm
- This example also appears in Chapter 3: *Research Training and Career Development*

- (E) (**FIC**, NICHD, ODS)

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 2: *Minority Health and Health Disparities*.
- (E) (NHLBI, NCMHD)

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 2: *Infectious Diseases and Biodefense*.
- (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 under three. 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIAID)s

Therapies to Treat and Prevent Food Allergies: The NIH Consortium of Food Allergy Research is developing immune-based approaches to treat food allergy, rather than to simply avoid food allergens. Basic studies are ongoing using mouse models to study how modified forms of peanut allergens protect against peanut-induced anaphylaxis. The five clinical sites of the Consortium are developing treatment and prevention strategies for food allergy, and they work to educate parents and health care providers regarding food allergies. An ongoing observational study is examining immune mechanisms, genetic factors, and environmental factors associated with the development of new food allergy to peanut and the loss of egg allergy to high-risk children. An interventional

study aims to determine the safety and immunologic effects of giving egg by mouth to egg-allergic children, with the goal of inducing immunological tolerance. Phase I clinical trials are assessing the safety of treating peanut-allergic subjects with either a modified form of peanut allergen or small amounts of peanut allergen under the tongue.

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

Prenatal Alcohol, Sudden Infant Death Syndrome (SIDS), and Stillbirth (PASS) Research Network: Following a 3-year feasibility study, NIH established this multidisciplinary consortium in order 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.

- For more information, see http://www.nichd.nih.gov/research/supported/pass.cfm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (**NICHD**, NIAAA)

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 joint and muscle (TMJ) 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 TMJ 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 http://www.nidcr.nih.gov/Research/ResearchResults/InterviewsOHR/TIS012006.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDCR)

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 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*, Chapter 3: *Clinical and Translational Research*, and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (**NIDDK**, CDC)

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: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (**NIDDK**, CDC, NIAID, NIEHS)

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 followup 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 2: *Cancer*.
- (I) (NIEHS)

Cognitive and Emotional Health Project: The Healthy Brain: The purpose of this initiative is to assess the state of longitudinal and epidemiologic 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://trans.nih.gov/CEHP/CriticalEvaluationStudyReport.pdf
- For more information, see http://trans.nih.gov/cehp/
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (**NINDS**, NIA, NIMH)

HIV/AIDS Epidemiological and Long-term Cohort Studies: NIH supports epidemiologic 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 between 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 www3.niaid.nih.gov/about/organization/daids/daidsepi.htm
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Life Stages, Human Development,*

and Rehabilitation.

- (E) (**NIAID**, NICHD)

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 man-made environments 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, the NCS will identify factors underlying conditions ranging from prematurity to developmental disabilities, asthma, autism, obesity, and more. The study is led by a consortium of Federal agencies including NICHD and NIEHS at NIH, CDC, and EPA.

- For more information, see http://www.nationalchildrensstudy.gov/
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (I) (NICHD, NIEHS)

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 & 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.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5903:0:15,3046:1:0:0:::0:0
- For more information, see http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/moba/index.cfm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
- (I) (NIEHS)

Databases for Cervical Cancer Research: NIH has developed data analysis and image recognition tools for studying biomedical images of human papillomavirus (HPV) infection and cervical neoplasia. Image data include 100,000 cervicographs (high-definition cervical photograph), 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: *Disease Registries, Databases, and Biomedical Information Systems*, and Chapter 2: *Cancer*.
- (I) (**NLM**, NCI)

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 2: *Minority Health and Health Disparities*.

- (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) compared to White subjects (5.5 percent). Among persons 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 2: *Minority Health and Health Disparities*.
- (E/I) (**NHLBI**, NEI)

Summary of Research Activities by Key Approach and Resource

Genomics

In the early 1950s, the race to discover the structure of DNA was on. At Cambridge University, James Watson and Francis Crick made physical models to narrow the possible DNA structure. At King's College in London, Maurice Wilkins and Rosalind Franklin took an experimental approach, looking at x-ray diffraction images of DNA. Based partially on Rosalind Franklin's data, Watson and Crick built a model in which each strand of the DNA molecule was a template for the other, allowing DNA to make identical copies of itself at each cell division. The structure so perfectly fit the experimental data that it was almost immediately accepted. Elucidating the structure of DNA has been called the most important biological work of the last 100 years, and the field it opened may be the scientific frontier for the next 100.

Introduction

Genomics is the study of an organism's entire genome—the complete assembly of DNA (deoxyribonucleic acid), or in some cases RNA (ribonucleic acid)—which transmits the instructions for developing and operating a living creature. It focuses not just on individual genes but also on the functioning of the genome as an interrelated network, and it is a new, rapidly expanding field of biological and medical research.

DNA is made up of four chemical compounds called "nucleotides"—adenine, thymine, guanine, and cytosine—denoted by the letters A, T, G, and C. These nucleotides are assembled in two parallel strands that are connected in the form of a double helix, and each nucleotide in one strand always links to the same partner on the other strand: A always pairs with T; C always pairs with G. Each of these pairings is referred to as a "base pair." The human genome consists of about 3 billion base pairs, packaged into 23 sets of chromosomes, in virtually every cell in the body. Identifying the base pairs—and thus the letters—and the order in which they appear on any stretch of DNA is called "sequencing" that segment. DNA's double helical structure was discovered in 1953, and the human genome was fully sequenced just less than 50 years later, in 2003, after a 13-year, U.S.-led international effort called the Human Genome Project.

The sequencing of the human genome generated immense scientific excitement. It provided a new means of analyzing the functions of cells, tissues, and systems in the body and understanding and attacking the causes of disease. It enabled broad new scientific disciplines such as proteomics, the study of the structure and function of all the proteins produced by the body in response to instructions carried by the genes. It also gave many people the impression that all the questions of biology had been answered and that the genome had been fully decoded. This is not so. Sequencing the genome indicated the order of the letters; the question now is how precisely the words are written and what they mean.

Every human disease or disorder has a genetic component. Some heritable diseases, such as cystic fibrosis or Huntington's disease, result from mutations to single genes—changes that disrupt their proper functioning. The role of genes is more complicated in most other diseases. Some diseases arise as a result of spontaneous gene mutations that occur during a person's lifetime; others are caused by complex cascades of changes in gene expression triggered by environmental factors. Differences as small as one letter in a stretch of DNA can cause disease directly or make people respond differently to particular pathogens or drugs. A single DNA base change in the "spelling" of the genome sequence—called a single nucleotide polymorphism, or SNP—also can help

researchers track down genes involved in disease. Heart disease, asthma, and myriad other diseases appear to have multiple genetic factors, although all the genes involved have not been identified. Many types of cancer are caused by damage to one or more genes that leads to further mutations as cells divide.

Scope of NIH Activity in Genomics Research

Virtually every NIH IC engages in some genome-related research. NCI sponsors an array of gene-oriented projects, including an effort to compile The Cancer Genome Atlas, a catalogue of the many genetic changes that occur in cancer cells. NHLBI supports a major epidemiological project, the Framingham Genetic Research Study, to search for genetic links to disease in 9,000 study subjects across three generations. NIAID's Microbial Genome Sequencing Centers program is sequencing the genomes of many disease-causing microorganisms, including the fast-mutating RNA virus that causes influenza, seeking information that may help design vaccines or therapies to avert worldwide pandemics.

NIH researchers and grant recipients also are sequencing other nonhuman genomes, and not just the genomes of our mammalian relatives such as the chimpanzee, to highlight stretches of DNA that have remained similar across species for millions of years. Such similarities—or small differences in otherwise similar stretches of DNA—can help determine the roles and importance of particular sequences, and also may point the way toward therapies for diseases that affect humans. AIDS, caused by the human immunodeficiency virus, is one such disease.

An international consortium led by NHGRI has begun an effort to identify every functional element in the human genome, called the Encyclopedia of DNA Elements (ENCODE) project. Initial results reveal that genes do not operate independently but are part of a complex network, and that most of the genome's "noncoding" DNA, that is, sequences that are not part of a gene, is not "junk" but appears to have important, heretofore unknown, functions.

Toward an Era of "Personalized Medicine"

ENCODE and other NIH programs also aim to develop new technologies to reduce the cost of genome sequencing and otherwise aid in understanding the human genome. This includes the development of computer techniques and software to organize and analyze immense amounts of data, which are made available free of charge to all qualified researchers via public databases. When the Human Genome Project began in 1990, DNA sequencing cost about $10 for each base pair. By 2007, that had been reduced to less than 1 cent, or less than $20 million for sequencing a full human-sized genome.

Ultimately, NIH would like to reduce the cost of sequencing an entire human genome—all 3 billion base pairs—to $1,000 or less, making possible a new era of "personalized medicine." When costs are reduced to the point that sequencing an individual patient's genome is feasible, and when the impact of small genetic changes on disease progression and therapy is better understood, clinicians will have powerful new methods with which to defend their patients' health.

Summary of NIH Activities

In FYs 2006 and 2007, NIH made significant progress toward exploiting the raw data of the human genome sequence and translating it into advances in human health. NIH-funded researchers and other scientists have laid the foundation for a scientific revolution—a truly new paradigm that will soon change medical research and the practice of medicine itself, moving beyond a one-size-fits-all approach. Most of the changes in practice and research that will matter for human health and our understanding of basic human traits have not yet happened. However, the next decade will yield the fruits of this foundational work, leading scientists increasingly closer to better means for preventing, diagnosing, and treating disease.

Among NIH's key accomplishments in the field of genomics in the FY 2006-2007 period were:

- Collaborating in the completion of the haplotype map of the human genome, known as the "HapMap": An

international effort, the HapMap identifies the location of more than 3.1 million SNPs along the 3 billion bases of human DNA. SNPs are relatively common variations that serve as markers for whole neighborhoods of gene-carrying DNA. As such, they are signposts by which researchers can compare individuals' genomes and hunt for genetic mutations that may be involved in disease.

- Confirmation that the genome is not a simple string of independent genes, but rather a complex network, for which the elements and functions are still incompletely understood: In a program that is still ongoing, the international ENCODE project (the acronym stands for " **ENC**yclopedia **O**f **DNA E**lements") conducted multiple analyses of carefully selected DNA segments totaling approximately 1 percent of the human genome—about 30 million base pairs—in an attempt to identify every functional element and to figure out which methods worked best for identifying functional elements. ENCODE's next phase is to determine the functions of the other 99 percent of the genome. NIH has launched a similar project, dubbed "modENCODE," to apply the same strict scrutiny to the genomes of two common laboratory model animals, the fruit fly *Drosophila melanogaster and the round worm Caenorhabditis elegans.*
- Full sequencing of additional vertebrate and nonvertebrate animal genomes: Completed vertebrate animal genomes include those of the dog, the horse, the cow, the opossum, the honeybee, and two nonhuman primates—the rhesus macaque and the chimpanzee. By 2007, NIH and NIH-funded centers also had sequenced thousands of different viruses, hundreds of bacteria, and many unicellular parasites, including two that cause malaria—not to mention two mosquito species, one a vector for human malaria, the other for avian malaria. Such data enable scientists to compare the genomes of different organisms and identify elements that are similar in many species. Scientists suspect that genetic elements that have remained similar in different species over millions of years of evolution have important functions; thus, similarities between different species' genomes may provide clues about human disease processes. Sequencing of other nonhuman genomes also is a major ongoing NIH program.
- Development of new laboratory tools and methods, and new computer algorithms for analyzing immense quantities of data, in order to reduce the cost of genome sequencing: A major goal of NIH sequencing programs is to reduce costs so that in time, physicians will be able to collect and use genomic data from their own patients—moving sequencing from blue-sky science to bedside therapy.
- Confirmation that genetic differences underlie much of an individual's response to medications, and that those genetic differences can be detected and potentially used to develop personalized treatment approaches: For example, in recent research, patients with two copies of a particular version of the serotonin 2A receptor gene responded significantly better to the antidepressant drug citalopram, a selective serotonin reuptake inhibitor, than did patients with different versions of the gene. Some day, such analyses could allow physicians to choose drugs tailored to individual patients rather than by a one-size-fits-all approach.
- New tests for diagnosing once-puzzling diseases and potential new therapies to treat them: Identifying the gene or genes involved in a disease can help scientists understand how the defect results in malfunction and thus point the way toward treatments. This approach is still new, but shows promise. For example, in 2003, NIH researchers identified the gene responsible for Hutchinson-Gilford progeria syndrome, which causes premature aging and heart disease in children and usually causes death by the teen years. They discovered that a single point mutation—a one-letter misspelling—in the gene known as *LMNA* produces a defective structural protein, which in turn causes misshapen nuclei in the patient's cells. Two years later, scientists following up on the discovery showed that an existing anticancer drug might correct the damage. Now, a 3-year clinical trial of this potential therapy for a devastating childhood disease is under way in the NIH Clinical Center.

The HapMap and Genetic Variation

Completion of the first phase of the HapMap in October 2005 by an international consortium of hundreds of researchers in six countries was one of the most significant developments in genomic research since the sequencing of the human genome in 2003.

The HapMap is the basic platform upon which most current genomic studies of human diversity are now built. It details the location of millions of relatively common single-letter variations in the human genome, that is,

variations that occur in at least 5 percent of people. The HapMap achieved two important goals: (1) it discovered most of the common variants in the genome and (2) it determined how these variants travel in "neighborhoods," or haplotypes, making it possible to track only a small percentage of all of the variants directly, allowing the rest to be inferred. It enables researchers to conduct studies that were simply impossible just a few years ago. When the HapMap was published, a commentary in the journal Nature noted that it had "succeeded in a spectacular way."[7]

In the early trailblazing years of genetic research, scientists largely were limited to seeking the single genes involved in classic, Mendelian-inherited diseases. A disease caused by a single damaged or inactive gene—such as cystic fibrosis or sickle cell anemia—could be traced in family history and then laboriously hunted down by trial-and-error comparisons of genetic variation across hundreds of families. However, diseases that involve several genes, where no single gene has a very large effect, have eluded such analysis, and most, if not all, human diseases involve a complex interaction of multiple genes. This is further complicated by the interactions of genes with environmental factors such as exercise, stress, and exposures.

The HapMap, together with advanced sequencing technology, now enables researchers to seek out the genetic roots of common, complex diseases by comparing and contrasting hundreds of thousands of points of variation among people. Thus, NIH-funded researchers have pioneered a whole new approach to genetic studies, called genome-wide association studies (GWAS, pronounced "gee-was").

The Big Picture: Genome-Wide Association Studies

GWAS examine not just a single stretch of DNA or the expression of a protein in a laboratory dish, but rather points of similarity and difference in the entire DNA sequences of people with or without particular diseases. In a typical GWA study, the genomes of 1,000 or more people with a particular disease are compared with the genomes of a similar number who are free of the disease. (Samples from many thousands of people are better, of course; the greater the number of individuals, the more accurate the study.) Theoretically, the "big picture" comparison of peoples' genomes will signal the presence of blocks of DNA that carry a gene or genes involved in the disease in question.

In the short time since they were devised, GWAS conducted by NIH or NIH-funded researchers have, among other discoveries:

- Identified a common genetic variation that significantly raises the risk of age-related macular degeneration. The finding strengthened our understanding of the link between the inflammation pathway and a devastating eye disease that often leads to blindness, and suggested a new treatment that is now under clinical study.
- Uncovered several genes that appear to play a role in bipolar disorder. One, which is active in the pathway through which lithium operates on the disorder, suggests a new treatment approach—seeking ways to regulate the enzyme involved, known as DGKH. Others may point scientists toward new directions for research.
- Located at least 10 sites of gene variants associated with type 2 diabetes—most of them never before identified. One of the sites includes two genes that had been studied in cancer, but never before associated with diabetes.
- Discovered three gene variants that may affect the ability of a person infected with HIV to control viral load and prevent or delay progression to AIDS. In addition to offering new approaches to anti-AIDS therapy, the apparent involvement of an immune system gene, *HLA-C*, may suggest a new avenue for research aimed at developing an HIV vaccine.
- Identified five new potential sites for breast cancer susceptibility genes. At least three of the five have been implicated in cell growth or cell signaling, rather than DNA repair or hormone metabolism, pointing the way toward new areas for basic research.

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[7] Goldstein DB, Cavalleri GL. *Nature* 2005;437:1241-2, PMID: 16251937

- Found a major site associated with prostate cancer risk on chromosome 8, with several different haplotypes that confer risk, and which may explain a substantial fraction of the increased risk in African Americans.
- Discovered additional variants of genes that increase the risk for colon cancer, Crohn's disease, rheumatoid arthritis, multiple sclerosis, Alzheimer's disease, gallstones, celiac disease, atrial fibrillation, glaucoma, lupus, coronary artery disease, and type 1 diabetes, among others.

With support from NIH and other sources, scientists will follow up on these discoveries through further genomic research to confirm and refine findings and, through nongenomic investigations, to discover preventions, diagnostics, and treatments.

A new, large-scale GWA study of cardiovascular and other chronic diseases is now under way in Framingham, Massachusetts. In collaboration with the Boston University School of Medicine, NIH is screening DNA from subjects enrolled in the long-running Framingham Heart Study—up to 500,000 analyses of DNA from 9,000 people who have been followed over three generations since 1948. The Framingham study has been a key source of knowledge about heart disease, stroke, and other chronic diseases; the new genome-wide association analyses will add immensely to understanding the genetic factors involved.

The genome-wide association approach also is at the heart of a major effort to explore the relationship between genes and the environment in many common diseases. The trans-NIH Genes, Environment and Health Initiative (GEI), will add an additional step to GWAS: It will monitor the differing environmental factors to which people in the study are exposed, as well as genomic differences, to determine not only which genes may be involved in particular diseases, but also what specific environmental influences trigger disease in susceptible individuals. NIH awarded its first GEI research grants in 2007; in the program's first year, NIH plans to sponsor eight GWAS, two genotyping centers and more than 30 environmental technology projects—including efforts to develop small environmental sensors that people can wear or carry, like cell phones or iPods, to measure environmental exposures. The environment includes not only the chemical environment but also exposure to the behavioral environments of dietary intake, physical activity, psychosocial stress, and addictive substances.

In 2006, NIH also launched a 3-year series of GWAS seeking genes that raise the risk of prostate and breast cancer, known as the Cancer Genetic Markers of Susceptibility project.

Supplementing NIH's research efforts, a unique public-private partnership known as the Genetic Association Information Network (GAIN) has begun funding additional GWAS analyses of common diseases, beginning in late 2006 with studies of schizophrenia, bipolar disorder, diabetic nephropathy, attention deficit hyperactivity disorder (ADHD), major depression, and psoriasis. Managed by the nonprofit Foundation for the National Institutes of Health, GAIN is funded by private-sector partners, including Pfizer, Affymetrix, Perlegen Sciences, Abbott, and the Broad Institute of Massachusetts Institute of Technology and Harvard University.

As with other genetic data produced by NIH or NIH-funded researchers, all data from GWAS—including data resulting from the public-private GAIN studies—are made freely available to biomedical researchers worldwide through databases maintained by NIH. The trans-NIH GWAS Policy, released in August 2007, includes establishment of a central data repository of de-identified genetic (genotypic and phenotypic) data, and creates a more uniform approach to expanding investigators' access to GWA study data. Implementation guidance was released to intramural and extramural scientists in November 2007, and the policy became effective on January 25, 2008. Under the new guidelines, information is deposited into databases immediately, rather than being held back for months until it is published in scientific journals. This accelerates data availability, thereby facilitating the development of better diagnostic tools and the design of new, safe, and effective treatments.

Decoding Cancer

Understanding and developing new treatments for human cancer has long been a major goal of genetic research. Since the 1990s, a growing number of individual genes that predispose an individual to cancer have been

identified, such as the breast cancer genes *BRCA1 and BRCA2*. But it has become clear that cancer is not a disease caused by a single gene. Instead, cancer is known to involve many different forms of out-of-control cell growth and to be influenced by many different genes. A few of these mutations are inherited from a person's parents, but most occur during a lifetime of cell division, or, in some instances, are caused by some external environmental factor. (In some cases, the external factor is known, such as cigarette smoking in lung cancer; however, even smoking does not explain all cases of lung cancer, nor do all smokers get lung cancer.)

In its continuing effort to unravel human cancers, in 2006 NIH launched The Cancer Genome Atlas. In a 3-year pilot project, scientists at more than a dozen institutions will sequence and analyze genetic changes in tissue samples donated by thousands of brain, lung, and ovarian cancer patients. They will try to identify the specific alterations in genes associated with cancer and determine the genetic signatures of different cancer subtypes. Some cancers develop slowly; others are aggressive. Some respond to a particular chemotherapy; others do not. If the effort succeeds, The Cancer Genome Atlas will be expanded to cover other types of cancer (see also the section on *Cancer* in Chapter 2).

NIH already assembles—and makes available to medical researchers worldwide—a vast collection of genomic data resources and computer tools for accessing and analyzing that data, through such efforts as its Cancer Genome Anatomy Project and the Mammalian Gene Collection.

Nonhuman Genomes

NIH also continues to fund sequencing of the genomes of nonhuman organisms. Sequencing projects under way include the orangutan, the gorilla, and the gibbon genomes. In addition, NIH sponsors an ongoing program of sequencing the genomes of microorganisms that prey on humans. These efforts provide insights not only into potential approaches to controlling these organisms, but also into basic understanding of DNA, genes, and genomes. For example, studies of fruit flies and the round worm C. *elegans* have, for decades, been a source of basic knowledge about genes and their function that have enlightened studies in humans. Rats and mice are also key laboratory model animals and are hardly irrelevant to human genetics; more than 99 percent of human genes have analogs in the mouse. Studies of other mammals also can cast light on human disease. For example, a study of the dog genome suggested a possible new connection between human cancer and a gene that had never before been considered as a cancer suspect. The 2007 study revealed that a single gene is the major determinant of a dog's size, from Chihuahua to Great Dane. That gene, *IGF-1*, which codes for the hormone insulin-like growth factor-1, is similar to a gene in humans. If *IGF-1* is so important to size regulation in dogs, researchers say, it also may be involved in cell proliferation, and possibly cancer, in humans.

As is the case with humans, scientists can learn even more when they have data from many representative microbes of the same kind. For example, NIH has collected and sequenced the whole genomes of more than 2,500 human and avian influenza samples. The data from this ongoing project may help researchers anticipate the frequent evolutionary mutations in the virus that make designing a vaccine so difficult. It also may enable them to predict whether, and when, the A/H5N1 avian flu virus will mutate into a form that can easily infect humans, and to design a vaccine to counteract it. The possibility of an avian flu breakout into humans raises fears of a disaster similar to the 1918 Spanish flu pandemic, which is estimated to have killed 1 to 2 percent of the total world population. In 2007, an NIH research team developed a strategy for predicting the mutations that would permit the avian flu virus to adapt to humans—as few as two mutations could do it—and it is now possible to monitor newly isolated viruses to assess whether this possibility is occurring.

Genome Sequencing and Technology

Virtually all NIH sequencing programs have a dual purpose. Their aim is not just to answer a conventional research question, such as what is the DNA sequence of this organism or that gene, but also to reduce the cost of sequencing itself, and to increase the speed and efficiency of the task of analyzing DNA sequences.

For example, a consortium of 11 teams of investigators known as the ENDGAME consortium—the acronym stands for Enhancing Development of Genome-wide Association Methods—is seeking new approaches to conduct GWAS,

aimed specifically at lowering their cost and enhancing their usefulness. The Large-Scale Sequencing Program, which involves several sequencing centers throughout the United States, not only produces sequence data on a wide range of organisms to answer research questions, but also seeks ways to cut sequencing costs.

NIH's Genome Technology Program focuses directly on the development of new methods for transcribing DNA sequences, comparing sequences to identify variations, and determining the effects of such variations on genetic function and thus human health. Such analyses require significant computer backup. Because the human genome comprises more than 3 billion DNA base pairs, there are more than 3 billion possible points of difference between the genomes of any two individuals, and a genome-wide association study may involve several thousand individuals. Without such analytic efforts—which DNA researchers call "annotating," and could not be accomplished without sophisticated and innovative computer programming—DNA sequences are simply disconnected strings of letters in an alien language.

Currently, the field is undergoing a revolution in sequencing technology. The cost of sequencing the entire genome of an individual human being has been reduced from several billion dollars to between $100,000 and $1 million. NIH's goal is to bring that cost down to $1,000—and to truly bring genomic science to the bedside. That era of personalized medicine may be only a few years away.

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

The Big Picture: Genome-Wide Association Studies

Genome-Wide Association Studies (GWAS) and Database of Genotype and Phenotype (dbGaP): In December 2006, NIH released the initial dbGaP dataset using genome-wide association study 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. In order 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 controlling for other factors, certain forms of the genes increased risk of AMD progression 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.

- (E) (**NEI**, NIA, NLM)

Genetic Association Information Network (GAIN): GAIN is a public-private partnership initiative that will elucidate the genetic factors influencing risk for many complex diseases. The resulting data will be made available in a central database managed by NIH for no-cost access by the scientific community. Of the six initial studies receiving funding through GAIN, four will target mental disorders: schizophrenia, bipolar disorder, major depression, and attention deficit hyperactivity disorder.

- For more information, see http://www.fnih.org/GAIN2/home_new.shtml
- For more information, see http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-07-060.html
- (O) (NHGRI)

Genome-Wide Genotyping in Parkinson's Disease (PD): NIH researchers ecently conducted genome-wide genotyping of publicly available samples from a cohort of 267 Parkinson's disease patients and 270 neurologically normal controls to identify any common genetic variability with significant effect on the risk for PD. The project has produced around 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 PD and other neurodegenerative disorders, and the genotypes from neurologically normal controls can be used as a comparison cohort for other studies, dramatically reducing the cost of future research.

- Fung HC, et al. *Lancet Neurology* 5:911-6, PMID: 17052657
- For more information, see http://www.nia.nih.gov/NewsandEvents/PressReleases/PR20060927parkinsons.htm
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (**NIA**, NINDS)

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 GWAS of complex diseases. ENDGAME investigators are developing and testing innovative, informative, and cost-effective study designs and 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 enhance greatly the utility of GWAS for increasing understanding about genetic variations and their role in health and disease.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (**NHLBI**, NCI, NHGRI, NIEHS, NIGMS)

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 the 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 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, see http://www.genome.gov/11511175
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Technology Development*.
- (E/I) (NHGRI)

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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH)

Gene Expression Changes in Facioscapulohumeral Muscular Dystrophy (FSHD): Results from a genome-wide scan of skeletal muscle biopsies suggest a link between eye blood vessel defects and muscle defects that characterize FSHD. Patient participants were recruited from the National Registry for Myotonic Dystrophy and FSHD Patients and 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (**NIAMS**, NCRR, NINDS)

Decoding Cancer

The Cancer Genome Anatomy Project (CGAP): The goal 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 2: *Cancer*.
- (E/I) (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/extramural consortia by creating strategic partnerships to accelerate knowledge about the genetic and environmental components of cancer induction and progression. Using 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. LTG will create opportunities for collaboration and data sharing in order to accelerate the translation of genomic findings into clinical interventions.

- For more information, see http://epi.grants.cancer.gov/Consortia/tablelist.html
- For more information, see http://epi.grants.cancer.gov/BPC3/cohorts.html
- For more information, see http://cgems.cancer.gov/index.asp

- For more information, see http://epi.grants.cancer.gov/PanScan/
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (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 catalogue, 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 2: *Cancer* and Chapter 3: *Technology Development.*
- (E/I) (**NCI**, NHGRI)

Nonhuman Genomes

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. 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 researchers reported a genetic variant that is a major contributor to small size in dogs, followed by a second study finding 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: 17530926S
- For more information, see http://www.genome.gov/25520294
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (I) (NHGRI)

Microbial Genomics: NIH has made significant investments in two large-scale programs to sequence microbes and genomes over the last decade. Sequenced pathogens include hundreds of bacteria, fungi, parasites, invertebrate vectors of diseases, and viruses (including those pathogens that cause anthrax, influenza, aspergillosis, tuberculosis, 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 (1) Microbial Genome Sequencing Centers, which rapidly produce high-quality genome sequences of human pathogens and invertebrate vectors of diseases, (2) The 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 over 2,800 human and avian influenza 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/research/topics/pathogen/default.htm
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E/I) (NIAID) (GPRA Goal)

Tools for Genetic and Genomic Studies in Emerging Model Organisms: In FYs 2006 and 2007, NIH funded eight grants that create genetic and genomic resources for model organisms whose genomes have been recently sequenced. These organisms include fish, invertebrates, and microbes used to understand human health, development, and disease. The resources include reagents and mutant lines, a center for high-throughput mutagenesis, genetic maps, databases, and stock centers.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-04-135.html
- (E) (NIGMS)

Human Microbiome Project: The human microbiome is the set of microbes that naturally inhabit the human nose, mouth, gut, vagina, and skin. The interactions between human hosts and these microbial communities at multiple body sites are known to be important for health, yet relatively little is known about them. The concept and plan for the NIH Roadmap Human Microbiome Project (HMP) was approved in 2007. By leveraging both the traditional approach to genomic DNA sequencing and the metagenomic approach (which allows the genomic sequencing of all microbes contained in a single sample), the HMP will lay the foundation for further longitudinal studies of human-associated microbial communities. Program initiatives are to characterize the genomes of the indigenous microbes of the human nose, mouth, gut, vagina, and skin, referred to as the "human microbiome," and determine whether individuals share a core human microbiome; to understand the relationship between the human microbiome and changes in human health; to develop novel technological and analytic tools needed to support these goals; to establish a data analysis and coordinating center and a resource repository; and to address the ethical, legal, and social implications raised by human microbiome research.

- For more information, see http://nihroadmap.nih.gov/hmp
- For more information, see http://www.genome.gov/26524200
- (E) (Roadmap–all ICs participate)

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 also now can systematically identify and target sequences within the DNA of *S. sanguinis* that are critical to the infectious process, providing 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 2: *Infectious Diseases and Biodefense*.
- (E) (NIDCR)

Genome Sequencing and Technology

Genome Technology and the $1,000 and $100,000 Genome Initiatives: DNA sequencing spells out the order in which our chemical building blocks are arranged, making DNA sequencing a powerful resource for biomedical research. Although DNA sequencing costs have dropped by more than three orders of magnitude since the start of the Human Genome Project, sequencing an individual's complete genome for medical purposes is still prohibitively expensive. Developing technology to make whole-genome sequencing more affordable would enable the sequencing of individual genomes to become part of routine medical care. The Genome Technology program supports research to develop new methods, technologies, and instruments to rapidly, and at low cost:

- Transcribe DNA sequences

- Check sequences for genetic variations (SNP genotyping)
- Aid research to understand the effects of genetic variations on genomic function

Additionally, NHGRI supports two types of sequencing grants: (1) "Near-Term Development for Genome Sequencing" grants support research aimed at sequencing a human-sized genome at 100 times lower cost than is possible today ($100,000) and (2) "Revolutionary Genome Sequencing Technologies" grants aim to develop breakthrough technologies that will enable a human-sized genome to be sequenced for $1,000 or less. Currently, only analyses of ~ 500,000 Single Nucleotide Polymorphisms (SNPs) are being performed commercially at this cost; an individual's complete genome sequence (~ 3 billion base pairs) would offer vastly more information.

- For more information, see http://www.genome.gov/10000368
- For more information, see http://www.genome.gov/19518500
- This example also appears in Chapter 3: *Technology Development*.
- (E) (NHGRI)

Large-Scale Sequencing Program: NIH's Large-Scale Sequencing Program funds three major research centers in the United States to conduct genetic sequencing. During and since the completion of the Human Genome Project, NIH-funded centers have used their industrial-scale enterprises to improve DNA sequencing methods, thereby substantially decreasing costs and increasing capacity. For many years, the Program has achieved twofold decreases in cost approximately every 20 months. One of the main projects now under way is the sequencing of the genomes of other primates, such as orangutan, baboon, gibbon, and marmoset (in addition to chimpanzee and macaque, which are complete). By comparing the human genome to that of other primates, researchers can find important information about both health and abilities that are uniquely human and those shared with other species. The Program also supports the genomic sequencing of human pathogens (organisms that cause disease in humans) and their vectors (the organisms that carry those pathogens). For other relevant NIH programs see previous section, Microbial Genomics. Also, many mammals are being sequenced to identify elements that are functionally important to human biology. These studies will undoubtedly unveil new biological insights to increase our understanding of how the human genome works.

- Rhesus Macaque Genome Sequencing and Analysis Consortium, et al. *Science*. 2007;316:222-34, PMID: 17431167
- For more information, see http://www.genome.gov/10001691
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NHGRI)

How Fast Is Evolution? Traditionally, scientists thought that evolution happened very slowly. They believed that it is quite rare to have major DNA changes (also called radical mutations) that benefit organisms and are passed on to future generations. Recently, NIH-funded researchers learned that in some cases, evolution can happen very quickly. By analyzing how DNA varies from person to person, and comparing human and chimpanzee DNA, the researchers discovered that radical mutations undergo a two-step selection process. Most mutations never make it past the first step, and slip out of the gene pool without being passed on to subsequent generations. But the rare mutations that survive this first cut spread rapidly throughout the species. These observations have relevance for our own species because, even though radical mutations represent only 10-12 percent of the differences between human and chimpanzee DNA, they may be responsible for some of the most significant differences between the two species.

- Gojobori J, et al. *Proc Natl Acad Sci U S A* 2007;104:3907-12, PMID: 17360451
- (E) (NIGMS)

Functional Genomics of Disease

Longevity Assurance Gene (LAG) Initiative and Interactive Network: The identification and functional characterization of genes and biological pathways controlling longevity and lifespan have advanced significantly, in

large part as a result of the efforts of scientists participating in the NIH-supported LAG Initiative and Network. The LAG Initiative has led to the identification of over 100 new longevity- associated genes, along with many other conserved biological processes and pathways that regulate longevity in a host of divergent species, including humans. These and similar discoveries are helping to illuminate disease processes, identify new predictive biomarkers, and facilitate identification of targets for preemptive drug therapy.

- (E) (NIA)

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 results of 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 over 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NHLBI)

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 (IBD). A genome-wide screen of samples collected recently identified three IBD susceptibility genes. The identification of such genetic factors can provide key insights into disease development and targets for designing more effective therapies for IBD.

- 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 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK)

A Multidisciplinary Approach to Nicotine Addiction: Nicotine addiction is the number one preventable public health threat, with 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 associated with nicotine addiction that could provide new targets for medications 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 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 ever 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 3: *Clinical and Translational Research*, Chapter 2: *Cancer*, and Chapter 2: *Neuroscience and Disorders of the Nervous System*.

- (E) (**NIDA**, NCI) (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. Several genes have been identified including GABRA2, ADH4, ADH5, and CHRM2, which 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 influencing 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: *Molecular Biology and Basic Sciences*, and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIAAA) (GPRA Goal)

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 the genetic predispositions underlying diseases like addiction. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as "gene chips" (e.g., the neurexin gene has been found to play a role in drug addiction). 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-environment interactions has recently been expanded to incorporate developmental processes, 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 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*.
- (E/I) (**NIDA**, NCI, NIAAA, NIMH) (GPRA Goal)

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 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 2: *Cancer* and Chapter 3: *Technology Development*.
- (E/I) (NCI)

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 the sequencing of any individual's complete genome affordable 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 2: *Chronic Diseases and Organ Systems*.
- (E/I) (NHGRI)

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 Sjögren'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*, Chapter 2: *Chronic Diseases and Organ Systems*, and Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIDCR)

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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDDK)

Environmental Genomics: NIH's Environmental Genome Project (EGP) was set up to catalogue all of the common variants, or single nucleotide polymorphisms (SNPs), in the coding and noncoding regions of the selected candidate

genes. These candidate genes were chosen to fall into eight categories: cell cycle, DNA repair, cell division, cell signaling, cell structure, gene expression, apoptosis (cell death), and metabolism. Since 2005, EGP has been expanded to include resequencing of factors controlling epigenetic modification of gene expression and nuclear receptors or other environmentally responsive genes. The newest NIH initiative on Environmental Genomics is supporting studies of the mechanisms of susceptibility to environmentally influenced diseases. This research is focusing on the critical common pathways through which environmental factors influence human health and the determinants of individual and population susceptibility to these stressors. Each application for this program was required to have a cross-stressor, cross-strain, and/or cross-species comparison depending on which comparative biology approach was most appropriate for the system of study. Two distinct approaches to utilizing comparative biology for understanding environmentally induced disease are used: (1) a genetically driven approach to define the genetic-environment interactions that contribute to the pathophysiologic responses and individual susceptibility or protection from disease and (2) a pathway and network-driven approach to defining molecular mechanisms that mediate the pathophysiological responses to toxins.

- For more information, see http://www.niehs.nih.gov/research/supported/programs/egp/
- (E) (NIEHS)

The NIH Pharmacogenetics Research Network (PGRN): NIH established the PGRN in 2000 to study how genes affect the way a person responses to medicines. The network includes 12 interdisciplinary research groups, each focused on a specific problem. Recently, one team (the Pharmacogenetics of Anticancer Agents Research Group) identified 63 genetic variants that regulate human responses to the anticancer drug etoposide. The drug can cause severe side effects, including leukemia. Knowing the genetic basis of these side effects will help scientists develop tests to identify which cancer patients can be treated safely with etoposide.

- Huang RS, et al. *Proc Natl Acad Sci U S A* 2007;104:9758-63, PMID: 17537913
- For more information, see http://www.nigms.nih.gov/Initiatives/PGRN
- (E) (NIGMS)

DNA Test for Charcot-Marie-Tooth Disease: Charcot-Marie-Tooth disease, one of the most common inherited neurological disorders, affects one 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (**NIGMS**, NINDS)

How the Genes in Cells Are Turned On and Off: In any cell, only a small fraction of the genes are activated. Scientists know that DNA is rolled around protein spools into structures called nucleosomes. They suspect that a gene's position on the nucleosome determines whether it is activated. Recently, NIH-funded investigators used state-of-the-art techniques to discover a DNA sequence that appears to mark the start of activated genes in yeast cells (a similar sequence is predicted to play the same role in human cells). The sequence appears at the same place on almost all of the thousands of nucleosomes in the study—a location that is accessible to the proteins that activate genes. Improper gene activation is linked to cancer and other diseases, therefore identification of a DNA sequence that regulates gene activation will help researchers prevent, detect, or correct problems with gene activation that are associated with these diseases.

- Albert I, et al *Nature* 2007;446:572-6, PMID: 17392789
- (E) (NIGMS)

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/press/stardgene.cfm
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH)

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 pre-teen 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 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/15515061
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (I) (NHGRI)

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/science-news/2007/tiny-spontaneous-gene-mutations-may-boost-autism-risk.shtml
- For more information, see http://www.nimh.nih.gov/science-news/2007/largest-ever-search-for-autism-genes-reveals-new-clues.shtml
- For more information, see http://www.nimh.nih.gov/science-news/2006/gene-linked-to-autism-in-families-with-more-than-one-affected-child.shtml
- For more information, see http://www.nimh.nih.gov/science-news/2007/new-tests-may-help-researchers-detect-genetic-basis-for-autism.shtml
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (**NIMH**, NCRR, NICHD, NINDS)

Resources

Rodent Model Resources for Translational Research: Mouse and rat models are the primary testbed for preclinical research and have played a vital role in most medical advances in the last century. Rodent models comprise about 90 percent of all animal studies enabling a wide range of genetic and physiological research on human disease. NIH

plays a major role in supporting the availability of normal and mutant mice and rats for translational research. Recent accomplishments include:

- Knockout Mouse Project (KOMP)—a Trans-NIH initiative to individually inactivate each protein-coding mouse gene to better understand the genetic functions of the estimated 22,000 mouse genes, which are, in many cases, very similar to human genes.
- KOMP Repository—established in FY 2007 to acquire and distribute the mouse models produced by the KOMP.
- Mutant Mouse Regional Resource Centers—distribution of genetically engineered mice increased by 50 percent in FY 2006 because of increased demand.
- Rat Resource and Research Center—acquisition and distribution of rat models increased by 50 percent in FY 2006 because of increased demand.

  - For more information, see http://www.genome.gov/17515708
  - For more information, see http://www.genome.gov/25521840
  - For more information, see http://www.mmrrc.org/
  - For more information, see http://www.nrrrc.missouri.edu/
  - For more information, see http://www.ncrr.nih.gov/comparative_medicine/resource_directory/rodents.asp
  - This example also appears in Chapter 3: *Clinical and Translational Research*.
  - (E) (NCRR)

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, serving 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: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
  - (E) (NIMH)

Database of Genotype and Phenotype (dbGaP): Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics, and other scientific data, NIH established dbGaP to house this growing body of information, particularly the results of GWAS, which examine genetic data of subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2007, dbGaP included results from more than a dozen GWAS, including genetic analyses added to the landmark Framingham Heart Study and trials conducted under the Genetic Association Information Network. dbGaP is to become the central repository for many NIH-funded GWAS in order to provide for rapid and widespread distribution of such data to researchers and accelerate the advance of personalized medicine.

  - For more information, see http://view.ncbi.nlm.nih.gov/dbgap
  - This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
  - (I) (NLM)

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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NHLBI)

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 (FHS), 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 over 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 FHS 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 FHS 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://www.nhlbi.nih.gov/new/press/06-02-06.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (**NHLBI**, NLM)

Conserved Domain Database and RefSeq: NIH's Conserved Domain Database (CDD) is a powerful means to deduce the function of newly discovered proteins. CDD is particularly valuable to researchers working on drug development and those requiring a synthesis of information on protein biological function, 3-D structure, and sequence conservation. In FY 2006 NIH met its GPRA goal of developing methods to classify at least 75 percent of proteins from sequenced genomes according to evolutionary origin and biological structure. NIH also met the FY 2006 GPRA goal of building a high-quality collection of reference sequences (the RefSeq database) to provide a unified view of the best available genetic information on organisms.

- Marchler-Bauer A, et al. *Nucleic Acids* Res 2007;35:D237-40, PMID: 17135202
- Pruitt KD, *et al Nucleic Acids* Res 2007;35:D61-5, PMID: 17130148
- For more information, see http://www.ncbi.nlm.nih.gov/RefSeq/
- For more information, see http://www.ncbi.nlm.nih.gov/Structure/cdd/cdd.shtml
- (I) (NLM) (GPRA Goal)

ENCODE: The ENCyclopedia Of DNA Elements (ENCODE) is an international research consortium organized by NIH that seeks to identify all functional elements in the human genome. The initial 4-year pilot phase has just been completed, and the consortium has published a series of papers describing a complex network in which genes and other regulatory mechanisms interact in complex ways. Other insights include the discovery that the majority of DNA in the human genome is transcribed into functional molecules, called RNA, and that these transcripts extensively overlap one another. These findings challenge long-held beliefs that the genome has small sets of genes and vast amounts of "junk" DNA. Until now, most studies have concentrated on the functional elements of specific genes, and have not provided information about functional elements in the vast majority of the genome that does not contain genes. ENCODE's exciting discoveries may well reshape the way scientists think about the genome and pave the way for more effective approaches to both understanding and improving human health.

- The ENCODE Project Consortium, et al. *Nature* 2007;447:799-816, PMID: 17571346
- For more information, see http://www.genome.gov/10005107
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NHGRI)

The Knockout Mouse Project (KOMP): The NIH Knockout Mouse Project (KOMP) is an NIH-wide effort to create a publicly available resource of knockout mouse mutations that can be used to study human disease. Knockout mice are strains of mice in which specific genes have been completely disrupted, or knocked out. By studying these mice, researchers can evaluate the effect of this systematic disruption of different genes on physiology and development. Understanding the effects of gene disruption in mice will provide powerful tools to develop better models of inherited human disease. NIH has awarded 5-year cooperative agreements for the creation of knockout mice lines to Regeneron Pharmaceuticals Inc. to a collaborative team from Children's Hospital Oakland Research Institute, and to the Wellcome Trust Sanger Institute in England. NIH has also recently awarded $4.8 million to the University of California, Davis, and the Children's Hospital of the Oakland Research Institute to establish and support a repository for the KOMP. The repository will enable many more researchers to have access to the knockout mice, and will ensure product quality for the 8,500 types of knockout mice currently available.

- Austin CP, et al *Nat Genet* 2004;36:921-4, PMID: 15340423
- For more information, see www.komp.org
- This example also appears in Chapter 3: *Technology Development*.
- (E/I) (NHGRI)

Genetics Home Reference: The Genetics Home Reference Web site provides basic information about genetic conditions and the genes and chromosomes related to those conditions. Created for the general public, the site was expanded to include summaries for more than 225 genetic conditions, more than 380 genes, all the human chromosomes, and information about disorders caused by mutations in mitochondrial DNA.

- For more information, see http://ghr.nlm.nih.gov
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (I) (NLM)

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. In a collaborative effort between the Office of the Surgeon General, NIH, the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality (AHRQ), and the Health Resources and Services Administration (HRSA), the U.S Surgeon General's Family History tool was created. 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 individuals to record health conditions that have affected their 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, see https://familyhistory.hhs.gov
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (O) (**OD**, NHGRI)

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 over 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 2: *Infectious Diseases and Biodefense*, and Chapter 3: *Molecular Biology and Basic Sciences*
- (I) (NLM)

Ethical, Legal, Social and Behavioral Issues

Genetic Factors in Health Disparities: A major concern in the era of genomic health care is to ensure that all racial, ethnic, and cultural groups benefit fully from genomic technology. One GPRA goal is to establish the role of genetic factors in three major diseases for which health disparities are noted. Building on the foundation of the Human Genome Project (HGP), NIH, as part of the International HapMap Consortium, has developed a way to scan large regions of chromosomes for variants (called SNPs, or single nucleotide polymorphisms) associated with increased risk of disease. Understanding the role of genetics in diseases characterized by health disparities will rely on such tools. As an example, the FUSION (Finland-United States Investigation of Non-Insulin-Dependent Diabetes Mellitus Genetics) study collected 820 million genotypes in 2006, which resulted in the identification of at least four new genetic variants associated with increased risk of diabetes and confirmed existence of another six. The findings boost to at least 10 the number of genetic variants confidently associated with increased susceptibility to type 2 diabetes—a disease that affects more than 200 million people worldwide, and a major cause of health disparities.

- Scott LJ, et al. *Science* 2007;316:1341-5, PMID: 17463248
- For more information, see http://nihperformance.nih.gov/
- (E/I) (NHGRI) (GPRA Goal)

Ethical, Legal and Social Implications (ELSI) Centers of Excellence for ELSI Research (CEERs): This center program has funded four full centers and three exploratory centers involving investigators in a wide range of disciplines to devise and employ interdisciplinary approaches to investigate ELSI issues such as:

- Intellectual property issues surrounding access to and use of genetic information
- Factors that influence the translation of genetic information to health care
- Conduct of genetic research that involves human subjects
- Use of genetic information and technologies in non-health care settings such as employment, insurance, education, criminal justice, or civil litigation
- Impact of genomics on concept of race, ethnicity, and individual/group identity
- Implications of uncovering genomic contributions to human traits and behaviors such as mental illness or aging for how we understand health and illness
- How different individuals, cultures, and religious traditions view the ethical boundaries for the uses of genomics

The use of CEERs resources and expertise to design and implement multifaceted and multidisciplinary investigations of particularly complex, persistent, or rapidly emerging ELSI issues is an important addition to ongoing genetic, genomic, and ELSI research efforts. Additionally, each CEER trains many young ELSI researchers each year.

- For more information, see http://www.genome.gov/10001618
- For more information, see Chapter 4: *NIH Centers of Excellence*.
- (E) (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 such as 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 followup 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NHGRI)

Genes, Behavior and the Social Environment: Moving Beyond the Nature/ Nurture Debate: This 2006 Institute of Medicine report was requested in order to examine the state of the science on gene-environment interactions as related to health, with a focus on the social environment. Report recommendations identified approaches and strategies to strengthen the integration of social, behavioral, and genomic research and training needs.

- For more information, see http://www.iom.edu/CMS/3740/24591/36574.aspx
- (E) (**OBSSR**, NHGRI, NIGMS)

NIH Revision Awards for Studying Interactions Among Social, Behavioral, and Genetic Factors in Health: These program announcements solicit applications for competitive supplements (revisions) to NIH grants to add a genetics/genomics component to a behavioral or social science project or the converse, i.e., to add a behavioral or social science component to a genetics/genomics project. This ultimate goal of this initiative is to elucidate how interactions among genetic/genomic, behavioral and social factors influence health and disease. The knowledge gained by such research will improve our understanding of the determinants of disease as well as inform efforts to reduce health risks and provide treatment.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-065.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-066.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-08-067.html
- (E) (**OBSSR**, NCCAM, NCI, NEI, NHGRI, NIA, NIAAA, NIAMS, NIDA, NICHD, NIDCD, NIDCR, NIDDK, NIMH, NINR, NINDS, ODS)

Summer Training Institute in Genes, Environment and Behavior Research: This training institute scheduled for summer of 2009 will target behavioral and social scientists at various career levels. The activity is designed to instruct the subjects in the theoretical and practical foundations of genetics and genomics and to introduce them to research on gene-behavior-environment interactions. The institute will help train a cadre of behavioral and social scientists capable of working in interdisciplinary teams to improve our understanding of how interactions

among genes, behaviors, and environments contribute to health and disease.

- (E) (OBSSR)

Summary of Research Activities by Key Approach and Resource

Molecular Biology and Basic Research

Over 30 years ago, the introduction of recombinant DNA technology as a tool for basic biological research revolutionized the study of life. Molecular cloning allowed the study of individual genes of living organisms; however, this technique was dependent on obtaining relatively large quantities of pure DNA. This problem was solved by the development of the polymerase chain reaction (PCR), which produced large quantities of a specific DNA sequence from a complex DNA mixture. Because of its simplicity and elegance, PCR transformed the way in which almost all studies requiring the manipulation of DNA fragments were performed. As described by Kary Mullis, who was awarded the Nobel Prize for Chemistry in 1993 for inventing PCR, the technique "lets you pick the piece of DNA you're interested in and have as much as you want." Because of its simplicity and ability to create hundreds of thousands of copies of a specific DNA sequence of interest, PCR allows for the routine yet highly efficient performance of most major molecular biology techniques including sequencing, cloning, and identifying variations in genes, including gene mutations that cause disease[8].

Introduction

Basic research is a major force driving progress across the biomedical and behavioral sciences, making it possible to understand the causes and progression of disease, intervene to prevent disease from occurring, develop better and more precise diagnostic devices and tests, and discover new treatments and cures. Basic research leads to fundamental insights that, on the surface, might not have an immediate or apparent application to human health, but are essential to understanding basic human biology and behavior in their normal and diseased states. It provides the foundation for responding to unexpected health crises. Whether the new insights come from blockbuster discoveries or an accumulation of incremental advances, history shows that over time, basic research yields inestimable rewards. Thus, it is a critical component of the Nation's public investment in research and is a central feature of each IC's research program. The importance of basic research to new interventions cannot be overestimated.

Basic research involves and relies on many scientific disciplines, including genomics, proteomics, endocrinology, immunology, genetics, epidemiology, neuroscience, behavioral, and social science, and cell, developmental, and vascular biology—to name a few. Importantly, basic scientists and clinical researchers frequently work together to translate research findings from bench to bedside and back.

As an influential component of basic research, molecular biology focuses on the formation, structure, and function of macromolecules—very large molecules that consist of many smaller structural units linked together. Macromolecules including proteins and nucleic acids—such as DNA and RNA—are involved in critical biological functions such as cell replication and storing and transmitting genetic information. The study of macromolecules provides information about structures that are essential to life. Such study yields knowledge of the molecular components of the cells of all types of organisms and the complex ways in which these molecules are organized, regulated, and interact, and provides essential insights for understanding and eventually controlling a wide range

[8] NIH did not fund Mullis's Nobel Prize-winning research, although it did fund other research by Mullis, and NIH-funded research laid the foundation that made Mullis's invention of PCR possible.

of human diseases.

Some researchers focus on individual or a few proteins, whose functions or structures, particularly if disrupted, may play key roles in specific diseases. Meanwhile, other researchers are engaged in “proteomics,” which entails integrating analytic technologies to identify and measure levels of large sets of (instead of individual) proteins. Scientists then study their interactions and how their levels fluctuate under various conditions. These basic efforts are helping to determine how such sets of proteins might change with the onset and progression of specific diseases, often providing insights about ways to intervene in the patient.

Molecular biology, like other areas of basic biological research, depends on harnessing the expertise and skills of allied disciplines such as physics, chemistry, mathematics, computer science, and engineering.

Every IC embraces basic research as essential to furthering the NIH mission—improving health. Although many ICs, such as NIAID and NCI, focus on research fundamental to specific diseases and organ systems, others, such as NIEHS and NIGMS, have missions that mandate they support basic research across a wide range of specialized disciplines. Still other ICs, such as NIBIB and NHGRI pursue basic research in more targeted areas.

For example, basic research in infectious disease examines the mechanisms that pathogens use to invade and infect the body, the interactions between pathogens and the bodies they infect, the mechanisms bodies naturally use to fight pathogens, and the environmental and genetic influences on the spread and evolution of pathogens. Insights from such investigations provide the targets for candidate vaccines, diagnostics, and treatments.

Because cancers affect various cells, organs, and tissues throughout the body, basic research in cancer is aimed, for instance, at understanding immune and inflammatory responses, stem cells, DNA repair mechanisms, and the microenvironment enveloping tumors. Discoveries in these areas are leading to medical advances that help patients with particular types of cancer. Not long ago, for example, experts disputed the validity of immunotherapy as a way of treating cancer. (Immunotherapy stimulates or restores the ability of the immune system to fight cancer, infections, and other diseases.) Now, this approach is being used as one standard of care for treating several specific types of cancer, including leukemia, lymphoma, and melanoma. Similarly, efforts to understand basic molecular mechanisms for repairing DNA could help cancer patients recuperate more quickly after receiving radio- and chemotherapy, both of which damage healthy as well as cancer cells.

Efforts to understand the microenvironment of cancer cells complement efforts to learn more about how the broader environment and associated toxic agents can affect human health and contribute to diseases other than cancer. One emergent area of research sponsored by NIEHS involves studying how toxic substances in the environment can impinge on signaling pathways within our cells, sometimes disrupting biochemical pathways and leading to subtle stresses or outright disease.

As part of fulfilling its mission to support a wide spectrum of basic research, NIGMS funded Andrew Fire and Craig Mello, who shared the 2006 Nobel Prize in Physiology or Medicine. In studying the roundworm *C. elegans*, they discovered a type of double-stranded RNA molecule that silences genes in that organism. Other researchers soon learned that similar RNA molecules silence genes in other organisms, including humans. Now these molecules are being studied as potential treatments for specific diseases. Thus, basic research on a roundworm, of no obvious direct medical interest itself, furnished insights that soon could lead to novel treatments for a diverse array of diseases, including Huntington's disease, hepatitis B, and cancer, among others.

The 2007 Nobel Prize in Physiology or Medicine was awarded to two long-time NIH grantees whose work

underscores the power of basic research to stimulate progress in the treatment and cure of disease. NIGMS began supporting Mario Capecchi and Oliver Smithies in 1968 and 1973, respectively. Later, other ICs also provided support. Working independently, Capecchi and Smithies created an elegant and powerful gene-targeting method in mice that has become an indispensable tool for biomedical research. The method enables scientists to create "transgenic" mice, which contain specific insertions of extra genes from mice or other organisms. When transferred genes involve human diseases, the transgenic mice can serve as model organisms for studying those human disorders. Researchers also can use the gene-targeting technique to insert defective genes that "knock out" the normal versions. Once these are "knocked out," scientists can understand the importance of these genes to normal function or disease. Mice developed with this technology are used for a wide range of medical research from basic studies of biological processes to investigations of, for example, cancer, heart disease, and cystic fibrosis.

Basic research often relies on studies in "model organisms" such as bacteria, fruit flies, or mice. Because human cells contain the same molecular building blocks and pathways as those of most other living things, researchers can learn much about the way our cells work by studying these simpler organisms. Although seemingly removed from human health, historically, many productive routes to medical discoveries involve organisms that typically are far simpler to study than are humans.

In addition, because candidate diagnostics and therapeutics typically need to be validated in model systems—for example, by studying animals that are susceptible to the same or similar microbial pathogens that cause diseases in humans or that develop diseases similar to humans, the development of animal models of disease is an important element of basic research. NIH-supported researchers have developed animal models for corneal disease, cleft palate, hearing loss, blindness, and even mental retardation. Animal models can lead to the development of promising interventions that then are subject to further refinement and testing before being evaluated in clinical trials. Conversely, fundamental research focused on improving human health also can provide veterinary benefits. For example, basic studies of the role of immune factors in controlling herpes led to a vaccine for a deadly disease in chickens.

The long-term implications of basic research in bioengineering and imaging also are profound. NIBIB is pursuing the tools that will enable tissue engineering and regenerative medicine to become standard medical realities. Basic research in imaging techniques is fueling a wide array of new means of diagnosis and making a quantum leap in structure-based design of drugs, a method that cuts through the cumbersome and expensive screening processes.

Basic science can yield unanticipated benefits, as scientists make so-called serendipitous discoveries. For example, while creating compounds to clog proteasomes—cellular garbage disposal-like structures implicated in muscle wasting—scientists noticed that one of the substances had anticancer properties; this drug (Velcade™) is now used to treat multiple myeloma, the second most common blood cancer. As another example, while studying the structures of complex sugars, scientists developed prototypes of new drugs to help control blood clots, which can cause heart attacks and strokes during surgery. This unpredictability is intrinsic to the interconnectedness of biological systems and the rudimentary stage of our knowledge. And rather than randomness or caprice—serendipity is the beauty of biology. However, as stewards of the Nation's investment in health science, NIH does not count on the serendipity—that is, NIH never funds or justifies a project based on expectations for serendipity. Rather, serendipitous findings are an added bonus from research projects already deemed meritorious for their intended purposes.

Basic biomedical research also benefits other sectors of the economy. Many nonbiomedical industries have emerged as a result of or been enhanced by biomedical discoveries. For example, freeze-drying, which was developed to concentrate and preserve laboratory samples, is now widely used in the food industry. As another

example, basic studies of digestive enzymes led to food industry improvements including meat tenderizers, bread dough conditioners, milk coagulants for cheese production, and preservatives for juices.

Summary of NIH Activities

As noted above, the impact of any single basic research discovery may be quite wide, bearing on multiple other fields. Research on neuronal receptors is perfectly likely to inform understanding of viral receptors. The inherent unpredictability to basic research means that it is not easily compartmentalized. The examples below reflect the breadth and diversity of the basic research pursued by NIH-research that touches on the mission of every IC, and every disease, condition, and effort to improve health.

One critical area of basic research that aims to understand how genes turn off or on or malfunction is epigenetics. In epigenetics research, investigators focus on factors that affect genes at the molecular level but do not change the sequence of the basic building blocks of DNA. Because epigenetics is concerned with factors unrelated to DNA sequence, these efforts differ from conventional genomics and genetics. Factors that cause epigenetic changes can come from the environment or may be in the diet, or related to other influences. Moreover, they are linked to a broad range of illnesses. A recently developed NIH program, the Genes, Environment and Health Initiative, supports research to understand how environmental exposures might induce epigenetic changes, particularly in critical periods such as during pregnancy, early life, and puberty. Related NIH-supported research aims at understanding how epigenetic changes and variations occur at the molecular level. (Also see Chapter 1 for description of the Roadmap 1.5 Epigenetics/Epigenomics initiative, in the section titled “Roadmap 1.5 and the Common Fund Strategic Initiative Process.”)

Another example of NIH-supported basic molecular research is the Molecular Libraries Roadmap Initiative. This program, established in 2006, offers public-sector researchers access to tens of thousands of small (that is, low in molecular weight) chemical compounds to probe the functions of genes, cells, and biological pathways and their impact on health and disease. Already investigators have used this resource to explore a wide variety of biological activities specifically related to normal processes and disease, including inflammatory pathways, previously unknown signaling proteins, and changes in cellular phenotypes associated with disease. Other investigators are gaining leads for drug discovery through access to these compounds.

The recently established Nanomedicine Development Centers, another component of the NIH Roadmap, takes advantage of technology developments at the nanoscale (on the level of biological molecules and structures inside living cells). The goal of this 10-year program, now involving more than 120 scientists from 30 institutions working at 8 centers, is to understand and control the nanomachinery of life in order to diagnose or treat and prevent diseases and repair injured tissues.

Some molecular-level research focuses on how pain signals are transmitted. For instance, NIH scientists recently learned that a particular protein, cyclin-dependent kinase 5, plays a regulatory role in pain signaling affecting sensory nerves. Their findings suggest that new analgesic drugs that alter this protein's activity could prove beneficial in relieving pain. Separate research on cannabinoids is guiding the design of molecules that block pain more selectively and safely, with minimal side effects and low potential for abuse.

NIH is supporting several molecular-level research programs studying complex carbohydrates, or polysaccharides, which consist of many linked sugars that are attached to the surfaces of proteins and lipids that form the surface of cells. These sugar-containing molecules are involved in diverse cellular activities, including signaling, recognition, adherence, and motility. They also play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. The detection and analysis of such carbohydrates are considered critical for

basic and clinical research but are widely regarded as a very difficult challenge.

Some NIH-sponsored molecular-level research explores fundamental physiological processes. For instance, NIH-supported scientists recently identified a protein, PKD1L3, in sensory cells that plays a key role in forming channels specifically for detecting sour tastes. This advance may help scientists treat taste impairments and could lead to the development of better salt and sugar substitutes for the millions of Americans on restricted diets that help to control high blood pressure, diabetes, and obesity.

Other NIH-supported scientists recently found that patients with chronic periodontitis, or gum disease, overproduce a signaling protein known as SHIP, which plays an important regulatory role in immune cells, inducing them to tolerate instead of react against an endotoxin, whose presence is associated with chronic periodontitis and tooth loss. Yet other NIH-supported scientists are studying a molecular byproduct, called resolvin E1 (RvE1), that derives from omega-3 fatty acids. RvE1 dramatically alters the progress of microorganism-initiated periodontitis and other diseases that arise through overly active inflammatory responses.

Some basic molecular-level research entails studying changes in molecules that disrupt cells and thus lead to specific diseases. For instance, misfolded proteins in brain cells are implicated in several neurodegenerative diseases, including Huntington's, Alzheimer's, and Parkinson's. Misfolded proteins can, in turn, disrupt other normal proteins in brain cells, leading to their death. NIH-supported scientists now surmise that learning how to bolster cell-repair mechanisms could provide an approach for treating some of these degenerative diseases.

In addition to proteins, damage also can occur to DNA molecules in cells when they are exposed to factors such as ultraviolet light or environmental toxins, sometimes leading to cancer or other serious clinical problems. NIH-supported scientists recently identified a protein that triggers a “lock-down” response to double-stranded DNA breaks, and helps to explain how cells ordinarily maintain their genetic material but sometimes lose that control in the case of cancer. More broadly, the NIH Tumor Biology and Metastasis Program supports research to delineate molecular mechanisms and signaling pathways involved in tumor progression, cell migration and invasion, angiogenesis (the process by which new blood vessels are formed), and metastasis.

NIH supports a range of basic research projects exploring cells, which are the basic membrane-bound units that make up organisms, and investigating biological systems, meaning the interactions among several or many biological components within organisms that lead to complex effects and integrated behaviors, including at the metabolic, cellular, and organ levels.

For example, many basic research projects focus on embryonic and adult stem cells, with some emphasizing genetic approaches and others analyzing critical events in early human development. NIH-funded researchers recently discovered a genetic switch that enables embryonic stem cells to develop into recognizable cell types; this and similar critical insights are expected to advance research on regenerative medicine and may lead to new treatments for many conditions, including, potentially, Parkinson's disease and spinal cord injuries.

Another example of an NIH-supported effort focused on cellular development is the Beta Cell Biology Consortium, which is conducting research relevant to the development of therapies for type 1 and type 2 diabetes. The consortium is studying how insulin-producing beta cells are made, exploring the potential of stem cells as a source for making insulin-producing islet cells, and determining the mechanisms underlying beta cell regeneration.

Some cell-based research focuses on the thousands of different microbial species that naturally associate with particular anatomic sites within or outside the human body, including in the intestinal tract and on the skin. These studies will help differentiate microorganisms that help to maintain health from others that can cause disease. The

studies also are advancing understanding of how environmental factors affect such microorganisms and whether environmental factors affect host susceptibility to or severity of diseases that occur at those and other anatomic sites.

Of course, some microorganisms such as the influenza virus are well known to be pathogenic. The threat of the H5N1 influenza virus, which has been circulating in Asia and elsewhere, is of particular concern because this strain of virus, while not readily transmissible between humans, is highly lethal to those who become infected. As part of a broad-based effort to track and analyze this emerging viral threat, NIH established the Influenza Virus Resource, which includes a database containing sequence information for more than 40,000 influenza sequences including the sequences of more than 2,500 whole influenza genomes. Moreover, in 2007 NIH established six Centers of Excellence for Influenza Research and Surveillance to conduct research on both animal and human influenza viruses. These efforts will assist investigators in understanding the basic mechanisms by which influenza virus replicates and spreads, which ultimately could lead to better treatments or vaccines.

Research on the activity of influenza viruses is one among several basic science efforts that address the complexities of the human immune system. Another example is the Immune Tolerance Network, a consortium of more than 80 investigators who share the long-term goal of learning how to eliminate harmful immune responses, such as graft rejection, while preserving protective immunity against infectious agents and other disease threats. Similarly, the NIH Consortium of Food Allergy Research is using a mouse model to study how modified forms of peanut allergens protect against peanut-induced anaphylaxis and is conducting an observational study to examine immune mechanisms, genetic factors, and environmental factors associated with the development of new food allergy to peanut and the loss of egg allergy in high-risk young children. In addition, the six centers of the Cooperative Study Group for Autoimmune Disease Prevention are devoted to understanding immune homeostasis (physiological balance or equilibrium), a concept fundamental to preventing autoimmune diseases, with one emphasis being type 1 diabetes. In yet another effort that began in FY 2005, NIH supports research to better understand the underlying biological and physiological factors involved in asthma exacerbations. These insights ultimately could lead to the development of more effective treatments for this immune system-related condition.

Beyond the immune system, NIH is supporting systems biology research that is driven by both basic experimental and computational approaches. For instance, NIH sponsors efforts at seven interdisciplinary centers to develop predictive computer models for use in analyzing drug metabolism, host-pathogen interactions, organism development, and cell signaling. Similarly, the Integrative Cancer Biology Program is focusing on networks and systems genetic research to develop a more basic understanding of cancer through multidisciplinary research.

Genetics provides yet another systems approach to studying particular diseases or wider physiological systems. For instance, the Gene Expression Nervous System Atlas, or GENSAT, is a comprehensive effort to analyze where and when during development genes are active within the mouse nervous system. In addition, the genetically engineered mice used to generate the atlas are also proving to be a valuable resource. For example, researchers recently used mice from the GENSAT project to study mechanisms that kill nerve cells in patients with Parkinson's disease. Meanwhile, other genetics efforts in basic research are aimed at uncovering the cause of hereditary hearing loss and stuttering, identifying the genes involved in regulating sensitivity to alcohol, and analyzing the 400 or more genes involved in vision loss.

NIH supports the development or identification of many different animal models for use in studying a broad range of diseases and conditions. In mice alone, this ranges from the development of a genetically engineered mouse for studying several diseases affecting the surface of the eye to the use of aged and obese mice in studying the mechanisms controlling the lifespan.

Several basic research programs focus on angiogenesis, the process whereby new vessels form to supply specific tissues and organs with blood, as well as other disorders affecting blood vessels. For example, NIH-supported research in animal models showed that dietary omega-3 polyunsaturated fatty acids reduce harmful angiogenesis in the retina. In a separate effort, investigators are using mouse models to study the biological and chemical properties of the drug losartan, which is widely used to control hypertension, to determine whether it might also be useful for preventing life-threatening aortic aneurysms, which occur often among individuals with Marfan syndrome. Yet other NIH-sponsored basic research aims at developing novel synthetic replacements for damaged or diseased blood vessels. Further, NIH is sponsoring basic research into the lymphatic system and its function in health and disease; such research might lead to the development of new diagnostic methods and treatment interventions.

The NIH also supports basic research in neuroscience at the molecular, cellular, systems, and cognitive and behavioral levels to understand the development and function of the nervous system (also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2). This research in people and in animal models includes studies of the neurobiological mechanisms underlying pain, sensory perception, learning, and addiction, among other nervous system functions. One project in the neurosciences is developing a set of standardized measures of cognitive, emotional, sensory, and motor function that will help researchers compare and integrate data collected across different studies. Basic research in the neurosciences also includes efforts to develop tools to monitor or probe discrete brain systems. For example, NIH-supported investigators recently genetically engineered neurons in mice and worms to express light-sensitive genes from algae and bacteria, allowing for rapid and precise control over neuronal circuit activity with pulses of light. NIH also invests in research in the behavioral and social sciences, with a goal to better understand social and cultural factors affecting health and illness.

Complementing these efforts, NIH supports a substantial portfolio of multidisciplinary research on mind-body interventions, such as meditation and Tai Chi Chuan, including basic research to understand the biological response to such interventions. Other projects involving complementary and alternative medicine focus on Alzheimer's disease and dementia, and include evaluations of the biological and biochemical consequences of the use of natural products such as an omega-3 fatty acid, *Ginkgo* biloba, and a component of pine trees. Still other projects are elucidating the fundamental mechanisms of turmeric extracts and green tea, used for treating conditions such as rheumatoid arthritis and obesity-associated insulin resistance, respectively. These basic research studies in animal models provide the foundation for future translational and clinical research.

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 at the Molecular Level

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 proinflammatory 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: *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (**NIDA**, NINDS)

Environmental Influences on Epigenetic Regulation: The field of epigenetics (gene expression and heritability unrelated to DNA sequence) is uniquely related to environmental health sciences. Almost all known factors causing epigenetic change are from the environment, diet, or supplements. Epigenetic mechanisms are being linked to multiple illnesses, including cancer, cognitive dysfunction, and respiratory, cardiovascular, reproductive, autoimmune, and neurobehavioral diseases. Recently, NIH developed a program in epigenetics that supports research to understand how the epigenome is affected by environmental exposures and how this affects human health. This field promises to shed light on how early life exposures can lead to disease later in life. One purpose of this program is to identify critical windows of susceptibility to epigenetic changes, particularly during pregnancy, early life, and puberty; this will help us develop biomarkers of early exposure, as well as identify possible therapeutic strategies to prevent later disease. Projects currently being supported by this program include epigenetic modulation of DNA repair during breast carcinogenesis and progression, gene silencing in mammalian cells induced by environmental exposure, impact of nongenetic factors on breast cancer susceptibility gene functions, and epigenetics of human cancer from chronic radiation exposure.

- For more information, see http://grants1.nih.gov/grants/guide/rfa-files/RFA-ES-05-007.html
- For more information, see http://grants2.nih.gov/grants/guide/rfa-files/RFA-ES-05-007.html
- (E) (NIEHS)

The Tumor Biology and Metastasis Program: This 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, with the goal of delineating the mechanisms of tumor-stromal interactions in human cancer.

- For more information, see http://tmen.nci.nih.gov/
- This example also appears in Chapter 2: *Cancer*.

- (E) (NCI)

Glycomics Technology Development, Basic Research, and Translation into the Clinic: Complex carbohydrates are ubiquitous, found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules is thus critical for basic and clinical research across the spectrum of health and disease, but is widely regarded as one of the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- Biomedical Technology Research Resources are developing and sharing cutting-edge technologies for analysis of carbohydrates in complex biological systems.

- Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.

- Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.

- A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.

  - For more information, see www.ncrr.nih.gov/glycomics
  - For more information, see www.functionalglycomics.org
  - This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development.*
  - (E) (**NCRR**, NCI, NHLBI, NIGMS, NINDS)

Shared Instrumentation Grant and High-End Instrumentation Programs: The goal of the NIH instrumentation programs is to provide new generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the $100,000-$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the $750,000-$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located on core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2006 and 2007 the SIG program funded a total of 264 grants for $95.2 million; the HEI funded a total of 39 awards for $55.9 million.

  - For more information, see www.ncrr.nih.gov/biomedical_technology/shared_instrumentation
  - This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development.*
  - (E) (NCRR)

ENCODE: The ENCyclopedia Of DNA Elements (ENCODE) is an international research consortium organized by NIH that seeks to identify all functional elements in the human genome. The initial 4-year pilot phase has just been completed, and the consortium has published a series of papers describing an intricate network in which genes and other regulatory mechanisms interact in complex ways. Other insights include the discovery that the majority of DNA in the human genome is transcribed into functional molecules, called RNA, and that these transcripts

extensively overlap one another. These findings challenge long-held beliefs that the genome has small sets of genes and vast amounts of “junk” or untranscribed DNA. Until now, most studies have concentrated on the functional elements of specific genes, and have not provided information about functional elements in the vast majority of the genome that does not contain genes. ENCODE's exciting discoveries may well reshape the way scientists think about the genome and pave the way for more effective approaches to both understanding and improving human health.

- The ENCODE Project Consortium, et al. *Nature* 2007;447:799-816, PMID: 17571346
- For more information, see http://www.genome.gov/10005107
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*.
- (E) (NHGRI)

Large-Scale Sequencing Program: NIH's Large-scale Sequencing Program funds three major research centers in the United States to conduct genetic sequencing. During and since the completion of the Human Genome Project, NIH-funded centers have used their industrial-scale enterprises to improve DNA sequencing methods, thereby substantially decreasing costs and increasing capacity. For many years, the Program has achieved twofold decreases in cost approximately every 20 months. One of the main projects now under way is the sequencing of the genomes of other primates, such as orangutan, baboon, gibbon, and marmoset (in addition to chimpanzee and macaque, which are complete). By comparing the human genome to that of other primates, researchers can find important information about both health and abilities that are uniquely human and those shared with other species. The Program also supports the genomic sequencing of human pathogens (organisms that cause disease in humans) and their vectors, the organisms that carry those pathogens. For other relevant NIH programs, see previous section, Microbial Genomics. Also, many mammals are being sequenced to identify elements that are functionally important to human biology. These studies will undoubtedly unveil new biological insights to increase our understanding of how the human genome works.

- Rhesus Macaque Genome Sequencing and Analysis Consortium, et al. *Science* 2007;316:222-34, PMID: 17431167
- For more information, see http://www.genome.gov/10001691
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development.*
- (E) (NHGRI)

Nanomedicine Development Centers (NDC): The structures inside living cells operate at the nanoscale (about 1/10,000 the thickness of human hair). Recent advances in nanotechnology, which refers to the understanding and control of materials at the nanoscale, have yielded new tools to probe and manipulate objects at the nanoscale. These tools, as well as a variety of newly engineered nanostructures, are starting to be used in biomedical research. Nanomedicine, an offshoot of nanotechnology, is a rapidly emerging, multidisciplinary field that was identified as one of the nine initial NIH Roadmap initiatives. In late 2006, NIH completed the establishment of a national network of eight NDCs after an intensive 2-year planning and application process that involved extramural stakeholders from scientifically and medically diverse fields. The overarching goal of these centers is to understand and control the nanomachinery inside living cells in order to diagnose or treat disease and repair tissue. The work at these centers, which involve over 120 biomedical researchers located in 30 institutions, 12 States, and 6 countries, is geared toward understanding the fundamental properties of intracellular structures with great precision so that highly specific treatment or possibly even replacement of these structures can be achieved with few or no side effects. Unlike traditional, translational research targeting a specific medical problem, these centers are beginning with basic science studies and, over a 10-year period, will apply their tools, technologies, and newly developed structures to a variety of disease or wound conditions that will be identified in parallel with, and as a consequence of, the technological developments. It is expected that this novel approach will stimulate the emergence of nanomedicine as a major contributor to improving human health in a variety of medical specialties.

- For more information, see http://nihroadmap.nih.gov/nanomedicine/index.asp
- This example also appears in Chapter 3: *Technology Development.*
- (E) (Roadmap—all ICs participate)

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 onto 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 2: *Life Stages, Human Development, and Rehabilitation.*
- (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, in mice, the critical developmental period of the palate, or roof of the mouth. 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 of nine mouse pups had complete reversal of the developing cleft, while 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 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIDCR)

Study on Forefronts of Science at the Interface of Physical and Life Sciences: In FY 2006, NIH cofunded a study by the National Academies to identify research Forefronts of Science at the Interface of Physical and Life Sciences. This study, to be completed in 2008, will identify and prioritize well-defined, large-scale, complex problems or grand challenges at the interface of the life and physical sciences and engineering that will drive research and nucleate the broad scientific community. It will also examine appropriate mechanisms for long-term high-risk research as well as approaches to catalyze greater cross-disciplinary collaborations. This study builds upon prior studies and conferences in this area led by Federal agencies and other National Academies efforts.

- (E) (**NIBIB**, NIGMS)

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.

- LopezJimenez ND, et al. *J Neurochem* 2006;98:68-77, PMID: 16805797
- Ishimaru Y, et al. Proc *Natl Acad Sci U S A* 2006;103:12569-74, PMID: 16891422
- Huang AL, et al. *Nature* 2006;442:934-8, PMID: 16929298
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (**NIDCD**)

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 counterregulate inflammation. This study provides evidence for the role of RvE1 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 2: *Chronic Diseases and Organ Systems.*
- (E) (**NIDCR**)

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 paper offers 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 2: *Neuroscience and Disorders of the Nervous System.*
- (I) (NIDCR)

New Molecular Targets to Halt Periodontal Bone Loss: Around 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; 20.8 million Americans suffer from diabetes and related complications, including increased incidence and severity of periodontitis: (1) 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, with the major effector being caspase-3. Inhibition of TNF-a or caspase-3 activity rescues cell death and restores repair capacity. (2) Discrimination between harmful microbes and commensal species is a critical property of the mucosal immune system, 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. Implication: 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 2: *Chronic Diseases and Organ Systems.*
- (E) (NIDCR)

Regulating Tumor Formation: Cells contain tiny pieces of RNA, DNA's chemical cousin, that were once thought to be no more than cellular junk. It is now clear that these microRNAs are important in regulating the activity of many genes in the cell. Two groups of NIH-funded scientists have found correlations between specific microRNAs and the ability of cells to form tumors. One group found that a specific family of microRNAs seems to help prevent cellular problems that can lead to cancer. The other group of researchers discovered that a particular chromosomal change—one that is found in human tumors—can disrupt the function of a certain microRNA. Specifically, the genetic change prevents the microRNA from keeping tight control over the activity of a tumor-promoting gene. This suggests that the loss of control is probably a critical step in tumor formation. A better understanding of the role that microRNAs play with respect to cancer may lead to new ways to prevent the development or spread of the disease.

- Mayr C, et al. *Science* 2007;315:1576-9, PMID: 17322030
- He L, et al. *Nature* 2007;447:1130-4, PMID: 17554337
- (E) (NIGMS)

Responding to Damaged DNA: Many factors can damage DNA, including ultraviolet light, environmental toxins, and cellular mistakes. When they divide, damaged cells can pass their faulty DNA to new cells. If the process continues, damaged DNA can build up inside the body, potentially causing cancer or other serious problems. To prevent this, the body uses powerful controls that lock down damaged cells, preventing them from dividing until their DNA is repaired. Recently, NIH-supported scientists identified a protein that triggers this lock-down in response to a specific type of DNA damage (double-stranded DNA breaks). These studies provide crucial insights into how cells maintain the accuracy of their genetic material and how they lose this control in cancer cells.

- Kumagai A, et al. *Cell* 2006;124:943-55, PMID: 16530042
- Yoo HY, et al. *J Biol Chem* 2007;282:17501-6, PMID: 17446169
- (E) (NIGMS)

Understanding How Protein Aggregation Causes Cell Death: Several neurodegenerative diseases—Huntington's, Alzheimer's, and Parkinson's—are characterized by clumps of misfolded proteins in the brain cells of patients. Normally, the body is very good at repairing or eliminating misfolded proteins, so it is not clear what goes wrong in these diseases. By studying the problem in roundworms, NIH-supported researchers learned that the abnormal protein found in Huntington's disease effectively jams the repair system. As a result, normal cellular proteins that misfold are not repaired. These misfolded, nonfunctional proteins accumulate, which triggers the aggregation of the disease protein. It is likely that the loss of these normal proteins, rather than the clumping of disease protein, is responsible for the death of brain cells. This research suggests that bolstering cellular repair mechanisms could be a promising therapeutic approach to these diseases.

- Gidalevitz T, et al. *Science* 2006;311:1471-4, PMID: 16469881
- (E) (**NIGMS**)

The Molecular Libraries Roadmap Initiative: The Molecular Libraries Roadmap Initiative, part of the NIH Roadmap, offers public-sector researchers access to high-throughput screening of libraries of small organic compounds that can be used as chemical probes to study the functions of genes, cells, and biological pathways. This powerful technology provides novel approaches to explore the functions of major cellular components in health and disease. The initiative is composed of several major components: The establishment of the Molecular Libraries Screening Centers Network (MLSCN), the Molecular Libraries Small Molecule Repository (MLSMR), a public Cheminformatics database (PubChem), and a series of technology development initiatives. In its second year, investigators within the Screening Center Network published several new screening approaches, including several that allow the chemical dissection of inflammatory pathways, one that has successfully identified multiple families of previously unknown signaling proteins, one that examines changes in cellular phenotype associated with disease using automated microscopy, and one that allows a range of compound doses to be screened at once. Each of these is expected to facilitate identification of compounds to probe biological activities and disease processes and identify leads for drug discovery. By December 2007, the 10 centers in the Molecular Libraries Screening Centers Network have entered screening data from more than 400 assays in the PubChem database at the National Library of Medicine.

- Rosen H, et al. *Trends Immunol* 2007;28:102-7, PMID: 17276731
- Inglese J, et al. *Nat Chem Biol* 2007;3:466-79, PMID: 17637779
- Zheng W, et al. *Proc Natl Acad Sci U S A* 2007;104:13192-7, PMID: 17670938
- Bologa CG, et al. *Nat Chem Biol* 2006;2:207-12, PMID: 16520733
- Edwards BS, et al, *Nat Protoc* 2006;1:59-66, PMID: 17406212
- Ramesh C, et al. *J Am Chem Soc* 2006;128:14476-7, PMID: 17090028
- For more information, see http://nihroadmap.nih.gov/molecularlibraries/
- For more information, see http://mli.nih.gov/mlscn/
- (E) (Roadmap—all ICs participate)

Basic Research at the Cellular and Systems Levels

Innovative Technologies for Engineering Small Blood Vessels: NIH has initiated a program of basic research studies to enlighten 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Technology Development.*
- (E) (NHLBI)

The Immune Tolerance Network: In 2007, NIH renewed support for the Immune Tolerance Network (ITN), a consortium of over 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 "reeducate" 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 to current methods that require years of biweekly injections. Current ITN studies include pancreatic islet transplantation for type 1 diabetes; approaches to slow or reverse 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 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*.
- (E) (**NIAID**)

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, while considerably more rare than cleft lip/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 currently affected. Exciting advances in genetic studies are shedding light on 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 information 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 offer 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 2: *Life Stages, Human Development, and Rehabilitation.*
- (E/I) (**NIDCR**, NIEHS)

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 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (NIDCR)

GENSAT—Gene Expression Nervous System Atlas: 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 timepoints 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 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (**NINDS**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, OBSSR)

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. 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 et al. 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
- For more information, see http://www.genome.gov/15515061
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Genomics.*
- (I) (NHGRI)

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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (**NHLBI**, NIAID) (GPRA Goal)

Interventions Testing Program: In a recent study, scientists demonstrated in aged obese mice that resveratrol, an activator of a family of enzymes called sirtuins, had better health and survival than untreated aged overweight mice. Future research will assess the safety and effectiveness of resveratrol-related drugs in humans. To further these and other investigations, NIH has undertaken a multi-institutional study to investigate a variety of agents with the potential to extend lifespan and delay disease and dysfunction in mouse models. This program is the centerpiece for a new NIH GPRA goal to "identify, by 2012, at least one candidate intervention that extends median lifespan in an animal model."

- For more information, see http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20061101Resveratrol.htm
- For more information, see http://www.nia.nih.gov/ResearchInformation/ScientificResources/InterventionsTestingProgram.htm
- (E/I) (NIA) (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. Several genes have been identified including GABRA2, ADH4, ADH5, and CHRM2, which 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 influencing 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 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (NIAAA) (GPRA Goal)

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. Multi-disciplinary teams are critical to integrating the disciplines of biology, medicine, engineering, mathematics, and computer science (e.g., computational biology). Equally important to our understanding of cancer is *systems genetic research* (systems biology + genetics). Networks of genes can be found and their associations tested and quantified, with

parallel association studies on relevant human populations.

- For more information, visit http://icbp.nci.nih.gov/
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development.*
- (E) (**NCI**)

Biomedical Technology Research Resources (BTRRs): The BTRRs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Resources and through intensive collaborations with other leading laboratories. The BTRRs are used annually by nearly 5,000 scientists from across the United States and beyond, representing over $700 million of NIH funding for 22 institutes and centers. As an example, optical technologies enable researchers to:

- Harness the power of light to "see" biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.

- Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

- For more information, see www.ncrr.nih.gov/biomedical_technology
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development.*
- (E) (NCRR)

National Ophthalmic Disease Genotyping Network (eyeGENE™): More than 400 genes are known to contribute to vision loss. New understanding of disease-related genes is leading to the next generation of vision care. With the remarkable opportunity afforded by gene therapy and other new treatment advances comes the challenge of identifying individuals who could benefit from these treatments. However, DNA testing remains expensive, time-consuming, and not widely available. To address this need, NEI created a partnership of laboratories across the vision research community and established eyeGENE to broaden accessibility of diagnostic genetic testing. These laboratories will facilitate research on genetic causes of eye disease; provide genotyping for patients in a centralized, secure, and certified process; and will provide a research repository of genetic material and diagnostic information. Currently, eyeGENE provides diagnostic testing for over 40 disease genes.

- For more information, see http://www.nei.nih.gov/resources/eyegene.asp
- (E/I) (NEI)

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 (PA) entitled 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 PA entitled 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 2: *Chronic Diseases and Organ Systems*.
- (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 PAs 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. 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 (R01)
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-361.html (R21)
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-004.html (R01)
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-005.html (R21)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E/I) (NIAAA)

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 2: *Infectious Diseases and Biodefense.*
- (E) (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 produce antibodies, and T cells, which can directly kill infected cells. Using high-throughput screening, several groups of researchers have identified, optimized, and developed adjuvants now in preclinical development.

- This example also appears in Chapter 2: *Infectious Diseases and Biodefense.*

- (E) (NIAID)

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 non-interventional 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 2: *Autoimmune Diseases.*
- (E) (**NIAID**, NIDDK)

NIH Stem Cell Task Force: In 2002, NIH established a Stem Cell Task Force to continually monitor the state of this rapidly evolving area of science. The purpose of the Task Force is to enable and accelerate the pace of stem cell research by identifying rate-limiting resources and developing initiatives to overcome these barriers to progress. The Task Force seeks the advice of scientific leaders in stem cell research about moving the stem cell research agenda forward and exploring strategies to address the needs of the scientific community. Over the past 5 years, under the leadership of the Task Force, NIH has supported a wide array of scientific programs designed to foster research on all types of stem cells, including human embryonic stem cells (hESCs), and is actively working to fund research in this blossoming field. For example, the Task Force has stimulated NIH-supported research by initiating Infrastructure grants to scale up and characterize hESCs eligible for Federal funding, developed training courses to teach stem cell culture techniques, established a National Stem Cell Bank to make hESC lines that are eligible for Federal funding readily available, and encouraged new investigator-initiated research through various means. The Task Force is also responsible for implementing Executive Order 13435, which encourages research on the isolation, derivation, production, and testing of stem cells that are capable of producing all or almost all of the cell types of the developing body and may result in improved understanding of or treatments for diseases or other adverse health conditions, but are derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus.

- For more information, see http://stemcells.nih.gov/policy/taskforce/
- (E/I) (**NIDCD, NINDS**, NCI, NCRR, NHLBI, NICHD, NIDCR, NIDDK, NIGMS, OD/OER, OD/OSP, OTT)

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 2: *Chronic Diseases and Organ Systems.*
- (E) (**NIDDK**)

Basic Research on Human Embryonic Stem Cells: Research on human embryonic stem cells (hESC) promises to illuminate critical events in early human development and, in the future, may revolutionize regenerative medicine.

In FY 2003, NIH funded the first of six Exploratory Centers for hESC research involving stem cell lines listed on the Human Embryonic Stem Cell Registry. Meetings at NIH in 2005 and 2007 highlighted the significant progress being made in this area by NIH-funded researchers. In FY 2007, NIH continued its support of research into the fundamental properties of hESC by funding two Program Project grants.

- For more information, see http://www.nigms.nih.gov/Initiatives/StemCells/
- (E) (NIGMS)

National Centers for Systems Biology: Systems biology is a new research field that integrates approaches from experimental and computational biology. Currently, NIH-funded researchers at seven interdisciplinary centers are developing predictive computer models to study areas such as drug metabolism, host-pathogen interactions, organism development, and cell signaling. These centers are both advancing their research fields and training the next generation of scientists.

- For more information, see http://www.nigms.nih.gov/Initiatives/SysBio/
- (E) (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 over 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*, Chapter 3: *Molecular Biology and Basic Science*, Chapter 3: *Genomics*, and Chapter 2: *Infectious Diseases and Biodefense.*
- (I) (**NLM**)

The Biomarkers Consortium: Launched through the NIH Program on Public-Private Partnerships in October 2006, the Biomarkers Consortium (BC) is a public-private partnership including NIH; the U.S. Food and Drug Administration; the Centers for Medicare & Medicaid Services; the pharmaceutical, biotechnology, diagnostics, and medical device industries; nonprofit organizations and associations; and advocacy groups. The BC is managed by the Foundation for the NIH. The BC will search for and validate new biological markers—biomarkers—in order to accelerate the delivery of successful new technologies, medicines, and therapies for prevention, early detection, diagnosis, and treatment of disease. Biomarkers are objective measures of risk, disease status, and/or health outcomes and include, for example, cholesterol and blood pressure as well known biomarkers of cardiovascular health. The BC structure will accommodate a number of discrete projects, each devoted to biomarker discovery, qualification, or use in targeted areas of disease-related biomedical and clinical science, with the ultimate aim to improve the public health. Projects will be proposed by members of the BC, academics, patient advocates, and the public, and will be developed and implemented according to their scientific merit, public health need and opportunity, and availability of support and funding.

- For more information, see http://www.biomarkersconsortium.org
- (E) (OD)

Animal Model for Corneal Diseases: NIH scientists have developed a genetically engineered mouse model for studying a number of eye diseases. In this mouse, the *Klf4* gene was deleted in the cornea, the conjunctiva, the eyelids, or the lens, to study the role of this gene in normal development and maintenance of the ocular surface. Deletion of the *Klf4* gene resulted in a reduced number of epithelial cell layers, irregular, defective cells and an absence of certain cell types. These mouse models will be used to study eye diseases and disorders that affect the surface of the eye, including dry eye, Meesmann's dystrophy, and Stevens-Johnson syndrome.

- Swamynathan SK, et al. *Mol Cell Biol* 2007;27:182-94, PMID: 17060454
- (I) (NEI)

Dietary Control of Angiogenesis in the Eye: The growth of new blood vessels, angiogenesis, can be a double-edged sword: while necessary for the normal development of tissues, uncontrolled angiogenesis can cause blindness in retinopathy of prematurity or diabetic retinopathy, or promote tumor growth in cancer. NIH-supported research in animal models showed that increased dietary intake of omega-3 polyunsaturated fatty acids reduces harmful angiogenesis in the retina. These findings suggest diet may provide a cost-effective method to prevent or ameliorate retinal vascular diseases.

- Connor KM, et al. *Nat Med* 2007;13:868-73, PMID: 17589522
- (E) (NEI)

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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
- (E) (NHLBI)

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 RhoGAP18B, 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.
- 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.

  - Rothenfluh A, et al. *Cell* 2006;127:199-211, PMID: 17018286
  - Urizar NL, et al. *J Neuroscience* 2007;27:4541-51, PMID: 17460067
  - This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
  - (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 a FAAH both as a potential susceptibility factor and as a therapeutic target for excessive alcohol consumption.

- Hansson AC, et al. *Neuropsychopharmacology* 2007;32:117-26, PMID: 16482090
- Blednov YA, et al. *Neuropsychopharmacology* 2007;32:1570-82, PMID: 17164820
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NIAAA)

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, over 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 Columbia, 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 2: *Neuroscience and Disorders of the Nervous System*
- (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 of stuttering.

- Riaz N, et al. *Am J Hum Genet* 2005;76:647-51, PMID: 15714404
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (NIDCD)

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 they 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 cleft lip and/or palate cases. 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 nearly twentyfold. 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.

- 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* 2006;80:76-90, PMID: 17160896
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (NIDCR)

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, if left untreated, craniosynostosis can distort the shape of the skull and portions of the face as well as cause hearing loss, blindness, and/or mental retardation. To better understand the causes of craniosynostosis, a team of NIH-supported researchers study the fusion of cranial sutures in mice. They suspect 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 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 wired into mesenchymal cells derived from

cranial sutures. This line of research potentially opens a new chapter in understanding the causes 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: Life Stages, *Human Development, and Rehabilitation.*
- (E) (NIDCR)

Life on Humans: A large number of microorganisms exist in us and on us, and some are crucial for our survival. Understanding their roles in health and disease is an important goal. Advances in molecular biology have made it possible to obtain a more comprehensive catalogue of the microbes that are present in environments such as the gastrointestinal tract or skin. NIH-supported researchers who examined microbes on the arms of six healthy subjects found that, although some microbes were common to all subjects, there was substantial diversity between individuals. Furthermore, the population of microbes present on a single individual changed over time, indicating that human skin supports a few "resident" microbes and many "transients." These studies are advancing the understanding of how environmental factors such as humidity, light exposure, and cosmetic use may affect microbes, and whether changes in these factors affect the susceptibility to or severity of skin diseases.

- Gao Z, et al. *Proc Natl Acad Sci U S A* 2007;104:2927-32, PMID: 17293459
- (E) (NIGMS)

Understanding Gene Regulation in Stem Cells: Stem cells are uniquely capable of being maintained indefinitely in an unspecialized state and of growing into specific cell types like muscle, blood, or nerve cells. Scientists hope to coax stem cells into specific cells that can treat diabetes, Parkinson's disease, spinal cord injuries, or other conditions in which specific cell types are not functioning properly. Recently, NIH-funded researchers discovered the genetic switch that enables embryonic stem cells to develop into recognizable cell types. This discovery addresses a fundamental question about the early development of mammals. It also brings researchers a step closer to the goal of using stem cells to treat a host of diseases.

- Lee TI, et al. *Cell 2006*;125:301-13, PMID: 16630818
- Boyer LA, et al. *Nature* 2006;441:349-53, PMID: 16625203
- (E) (NIGMS)

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 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NIMH)

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.neurosciencebluprint.nih.gov

- For more information, see www.nei.nih.gov/funding/app.asp#1b
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NEI)

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 2: *Neuroscience and Disorders of the Nervous System*
- (I) (NEI)

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 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NEI)

Basic Research in the Behavioral Sciences and in Complementary and Alternative Medicine

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 synch with the split-second pace of real-time neuronal activity. The novel technique borrows genes form 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 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development.*
- (E) (**NIDA**, NIMH)

Centers of Excellence for Research on CAM (CERC), Developmental Centers for Research on CAM (DCRCs), and International Centers for Research on CAM: These Centers bring cutting-edge scientific technology to programs of research on the usefulness, safety, and mechanisms of action of various CAM interventions. Based in collaborations between established biomedical research scientists and experts in CAM or traditional medicine, these programs are also aimed at enhancing the global state of research capacity on CAM. For example, the CERCs are led by scientists with outstanding research records who direct teams of investigators with both CAM and conventional scientific expertise. During the first 3 years of the CERC program, awardees have made sentinel advances in our understanding of the scientific basis for the effects of acupuncture through the use of modern brain imaging, and they have explored innovative approaches to the treatment of asthma with antioxidants and approaches based on traditional Chinese medicine (TCM). Other CERCs are focusing on (1) the study of acupuncture and TCM herbal treatments of arthritis, (2) the effects of mindfulness meditation on the progression of HIV/AIDS, and (3) the mechanisms of action of millimeter wave therapy (use of low-intensity millimeter wavelength electromagnetic waves) for a variety of chronic conditions. NIH will fund additional CERCs in late FY 2007.

- For more information, see http://nccam.nih.gov/training/centers/
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (NCCAM)

Basic Research on CAM: In addition to its focus on clinical investigation of complementary and alternative medicine interventions, NIH places a high priority on basic research aimed at filling important gaps in our knowledge about the mechanisms by which they may exert their effects. Recently released initiatives target this area of research. Examples include the following:

- "Omics and Variable Responses to CAM" utilizes genomic, proteomic, and metabolomic technologies to examine potential causes for variation in individual responses to CAM interventions (PAR-07-377).
- "Mechanistic Research on CAM Modalities Purported to Enhance Immune Function" examines the scientific basis for a common but generally unsubstantiated claim made on behalf of a number of CAM modalities (RFA-AT-06-004, RFA-AT-06-005).
- "Research on the Biomechanical, Immunological, Endocrinological, and/or Neurophysiological Mechanisms and Consequences of Manual Therapies" applies state-of-the-art science to investigating the biological basis for CAM interventions, such as spinal manipulation and massage. (PAR-06-312)

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

Basic Behavior in Animal Models: This program supports collaboration between behavioral scientists and molecular biologists to study basic mechanisms of behavior using animal models. The program also supports the development and enhancement of animal models to study normal or abnormal human behavior.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-096.html

- (E) (**NIGMS**)

Methodology and Measurement in the Behavioral and Social Sciences: This program supports basic and applied research to improve the quality and scientific power of data collected in the behavioral and social sciences. Among the FY 2006 and 2007 awards are projects developing improved measures of pain, physical, social, cognitive and neurocognitive functioning, quality of life, coping, and cultural and linguistic competence.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-060.html
- For more information, see http://obssr.od.nih.gov/Content/Research/Program_Announcements_%28PAs%29/Announcements.htm
- (E) (**OBSSR**, NCCAM, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIEHS, NIMH, NINDS, NINR, ODS)

Social and Cultural Dimensions of Health: This program supports research that elucidates social and cultural constructs and processes. This knowledge can be used to clarify the role of social and cultural factors in the etiology and consequences of health and illness, to link basic research to practice for improving prevention, treatment, health services, and dissemination, and to explore ethical issues in social and cultural research related to health. The currently funded projects examine multiple racial, ethnic, and other groups, and are investigating basic research topics such as discrimination, neighborhood design, stigma, socioeconomic status, physician decision-making, religiosity/spirituality, risk communication and sleep as they relate to behaviors, quality of life, palliative care, disparities, and other aspects of health.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-045.html
- (E) (**OBSSR**, NCCAM, NCI, NHGRI, NHLBI, NIA, NIAAA, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIMH, NINR)

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 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, with a particular emphasis on measuring outcomes in clinical trials and functional status in large cohort studies, e.g., epidemiological studies 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 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (**OBSSR**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR)

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

- 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 2: *Chronic Diseases and Organ Systems.*
- (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 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 in traditional Chinese medicine, experienced significant augmentation in levels of immunity to the virus that causes shingles following 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
  - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research.*
  - (E) (NCCAM)

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 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (NCCAM)

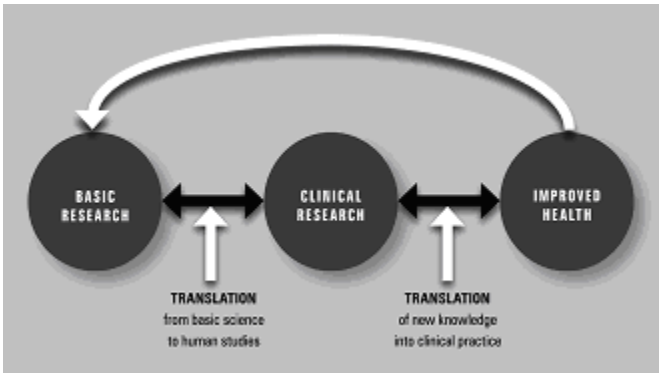
Summary of Research Activities by Key Approach and Resource

Clinical and Translational Research

Decades ago, population studies established that, while most human papillomavirus (HPV) infections clear up on their own, virtually all cases of cervical cancer were caused by HPV infection. National Cancer Institute (NCI) scientists Douglas Lowy, M.D., and John Schiller, Ph.D., saw this discovery as an opportunity to develop a vaccine to prevent cervical cancer. The NCI researchers used genetic engineering technology to isolate a single HPV protein and create virus-like spheres that were able to trigger an antibody response capable of protecting the body from the targeted types of HPV. After subsequent development and clinical trials, the unprecedented result is two FDA-approved vaccines that block infection by the major cervical cancer causing types of HPV. 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.

Introduction

Delivering new and effective treatments and disease prevention approaches to improve health depends on a research continuum that translates basic biomedical research findings into clinical practice and health care decision-making as rapidly as possible (Figure 1) (see also the section on Molecular Biology and Basic Sciences in Chapter 3). In this report, clinical and translational research are considered together because the two areas overlap, with translational efforts often focusing on overcoming barriers that impede the progress of clinical research.



Clinical research encompasses human subjects research (studies that involve direct interaction between investigators and human subjects or use of material of human origin, such as tissues, specimens, and data that retain information that would allow the investigator to readily ascertain the identity of the subject), epidemiologic (see section on Epidemiological and Longitudinal Studies in Chapter 3) and behavioral studies, and outcomes and health services research. Examples of clinical research include studies of mechanisms of human disease, clinical trials, and development of new technologies. Excluded from the umbrella of clinical research, however, are investigations that use anonymous specimens or data from human subjects; such studies would likely fall into the categories of basic or translational research.

Clinical trials, a subset of clinical research, often are considered the best method of determining whether interventions are safe and effective in people, including assessing the risks of adverse side effects and other complications. They are designed to answer specific research questions about a biomedical or behavioral

intervention. For example, treatment trials test experimental drugs or devices, new combinations of drugs, or new approaches to surgery or radiation therapy.

Prevention trials seek better ways to prevent a disease or to keep a disease from returning. Screening and diagnostic trials are conducted to find better ways to detect or diagnose diseases or health conditions. Finally, quality-of-life trials (or supportive care trials) explore ways to improve comfort and functioning for individuals with chronic illnesses or approaching the end of life.

Although other entities (e.g., pharmaceutical companies, nonprofit organizations) sponsor a sizeable body of clinical and translational research, the Federal Government plays a critical role in focusing on gaps that otherwise would remain unaddressed. NIH supports clinical and translational investigations unlikely to garner significant investment by other sources because of lack of financial incentives, for example, studies that address rare diseases, involve high costs and high risk, or are based on behavioral changes rather than drugs or devices.

NIH's ICs oversee a broad clinical and translational research portfolio that encompasses intramural and extramural programs. Nearly every NIH component supports clinical and translational research in strategic ways related to its mission. A highlight of the intramural program is the NIH Clinical Center, the Nation's largest hospital devoted entirely to clinical research. The Clinical Center logs more than 7,000 inpatient admissions and 100,000 outpatient visits annually. In order to be seen at the Clinical Center, individuals need to meet the eligibility criteria for a research protocol and agree to participate. The NIH extramural program, in addition to supporting both investigator- and NIH-initiated clinical and translational research, fosters collaborations among institutions, industry (e.g., pharmaceutical companies), and local communities; sets up innovative centers of clinical and translational research; underwrites animal and other preclinical studies; and develops new resources and tools for research. Moreover, the NIH extramural program supports important programs to expand capacity for clinical and translational research. A significant dimension of this capacity building is establishing and enhancing clinical research networks. Other vital aspects of this capacity building are training and career development initiatives to ensure that diverse pools of highly trained clinical and translational scientists are available in adequate numbers and in appropriate research areas to carry out the Nation's biomedical and behavioral research agendas (see the section on Research Training in Chapter 3). To accelerate and strengthen the clinical research process, a set of NIH Roadmap initiatives and follow-on programs are improving the clinical research enterprise. These include infrastructure for clinical research networks, outcome assessment tools, core services and resources, policy enhancement and harmonization, and a program of Clinical and Translational Science Awards (CTSAs). Thanks to such programs, a transformation of the clinical research enterprise is under way to speed new discoveries from bench to bedside to community.

Translational research drives progress along the research continuum and encompasses two separate stages. The first translational stage involves applying discoveries generated during research in the laboratory to the development of studies in humans. Such preclinical translational investigations often are carried out using animal models, cultures, samples of human or animal cells, or experimental systems. The second translational stage takes results from studies in humans and applies them to research on enhancing the adoption of best practices in the community.

Although sometimes referred to as bench-to-bedside research, translational research really is a two-way street. Basic research scientists provide clinicians with new tools for use with patients, and clinical researchers make new observations about the nature and progression of disease that often stimulate basic investigations. Research on new outreach approaches and the cost-effectiveness and real-world feasibility of prevention and treatment strategies are important aspects of this endeavor, as they provide the feedback necessary to ensure the practicality of interventions.

A special aspect of the scope of NIH activities in translational research is its collaboration with NIH's sister HHS agencies. Most ICs are engaged in such collaborations, which involve almost every other HHS agency. The collaborations include working groups and committees such as the Biomedical Imaging in Oncology Forum, the Joint Working Group on Telehealth, and the Health Literacy Workgroup; a wide range of translational research

such as projects on vaccine safety, child abuse and neglect, Diabetes Prevention Program Outcome Study, and Native American Research Centers for Health; database development and management such as the Stem Cell Therapeutics Outcomes Database; and health surveys such as the National Health and Nutrition Examination Survey (NHANES).

Summary of NIH Activities

NIH nurtures strategies for bringing basic research discoveries to human studies, optimizing the conduct of clinical research, facilitating the transfer of new knowledge gained through research into clinical practice, and aligning and reinforcing the entire continuum. The following sections delineate some specific strategies employed by the ICs to drive research along the research continuum and highlight a few examples from NIH's robust portfolio of clinical and translational research.

Preclinical Research: Translating Basic Science Discoveries to Human Studies

Before investigators can conduct human studies, much preliminary (basic and preclinical research) work must be done, and a supportive infrastructure must be in place. NIH equips preclinical translational scientists with research tools, enhances opportunities for collaborative research, and provides resources for developing and testing new drugs before progressing to human studies.

Research Tools and Resources

Among the research tools that NIH provides to promote preclinical translational studies are its myriad biosample and data repositories. A central repository allows additional studies on human samples and data collected during clinical studies, enhancing the value of each study and making optimal use of samples and data. It also ensures that samples are stored under uniform conditions and simplifies access to samples by the scientific community. Samples and data are labeled with codes, keeping the study subjects' information confidential. A notable example of such a repository was established through the Genetics of Kidneys in Diabetes (GoKinD) study. It facilitates investigator-driven research into the genetic basis of diabetic kidney disease by collecting, storing, and distributing genetic samples from patients with type 1 diabetes and diabetic nephropathy and from control type 1 diabetes patients without kidney disease. By gathering information and samples of the kind, quality, and quantity that individual researchers would be unable to collect on their own, GoKinD facilitates research on the genetics of diabetic kidney disease. (See also the section on *Disease Registries, Databases, and Biomedical Information Systems* in Chapter 3).

Animal models are critical components of translational research. They enable discoveries that are directly related to human health and are used in preclinical research to test therapies and vaccines. Resource Centers funded by NIH provide investigators with the animals, reagents, and information needed to develop animal models to uncover clues about the effects of specific genes on human health and disease and to gain insights into, for example, basic cellular processes. Additionally, NIH is establishing a new informatics resource to help researchers analyze preclinical research results of diverse studies involving animal models to determine whether a given new scientific discovery merits future development as a potential therapeutic approach (see also the section on *Technology Development* in Chapter 3).

Several preclinical cancer researchers are identifying and developing new biomarkers, which are physical, functional, or biochemical indicators of physiologic or disease processes. Some biomarkers play important roles in disease diagnosis, identifying patient populations that could benefit from particular therapies and monitoring treatment effectiveness. Through such programs as the Early Detection Research Network and the Strategic Partnering to Evaluate Cancer Signatures initiative, NIH brings together interdisciplinary teams at dozens of institutions to discover, develop, and test biomarkers and provide advanced analysis and tools that can be used to characterize an individual's disease or tumor so that personalized medical strategies can be developed.

Other translational research at NIH capitalizes on the intricate and interconnected pathways that link and enable communication among genes, molecules, and cells. These molecular pathways work together in a feat of biological

teamwork to promote normal development and sustain health. Many NIH-sponsored studies entail research into such pathways to determine how disturbances in them can lead to disease and to develop new therapies targeted at restoring normal function in disease-disrupted pathways. For example, one NIH initiative—Asthma Exacerbations: Biology and Disease Progression—was designed to improve understanding of what happens in the body at a molecular level to cause asthma flare-ups. The program could help identify and characterize molecular pathways that might provide a rational basis to develop new medications for preventing or treating such episodes.

Collaborative Science

Oftentimes, translational research can be streamlined or conducted more economically when scientists within NIH, private industry, academia, private practices, or other institutions work in partnership to complement each other's strengths and share costly resources or infrastructure. For this reason, NIH launched its Centers of Research Translation to unite basic and clinical research in a way that translates basic discoveries into diagnostic approaches and treatments through robust collaborative efforts. The first set of centers focuses on lupus, orthopedic trauma care, scleroderma, and a genetic form of rickets. In addition to these centers, various ICs also have entered into numerous public-private partnerships. One such public-private partnership is conducting animal studies to test promising compounds for treating fragile X syndrome (FXS), the most common cause of inherited mental impairment. By combining samples and data to increase their collective statistical power, collaborating scientists can conduct studies of rare diseases, such as FXS, more quickly than would be possible if they were working on their own.

Resources for Developing and Testing Investigational Drugs

NIH helps bridge the gap between drug discovery and clinical testing of promising new agents. Translating promising compounds into drugs for human use is an exacting task that requires very specific, interrelated activities. NIH provides state-of-the-science preclinical drug development resources. Specifically, NIH helps investigators by screening investigational drugs for possible activity against human disease, manufacturing them on a large scale, and clarifying regulatory issues so that FDA requirements are likely to be satisfied when the new investigational drugs are ready for testing in the clinic. One aspect of the NCI Experimental Therapeutics Program (NExT), for example, safely shortens the timeline for taking anticancer drugs from the laboratory to the clinic by combining NIH's expertise in drug development with that found in excellent research facilities.

Similarly, to move basic research on Alzheimer's disease into translational research and drug testing in clinical trials, NIH provides drug development and toxicology services to academic and small-business investigators who lack the resources needed to perform the required preclinical studies on promising therapeutic compounds. In addition, an entire menu of preclinical drug development contract resources is available through one of NIH's Roadmap initiatives, the Rapid Access to Intervention Development (RAID) programs. TheType 1 Diabetes RAID program is designed to facilitate translation to the clinic of novel therapeutic interventions for type 1 diabetes and its complications. Another RAID program is in place for investigational cancer therapeutics.

Clinical Research: Learning Which Interventions Work

Clinical research helps scientists develop and test interventions and new treatments. There are many types of clinical research. For example, some observational clinical research studies involve following a group of patients with a condition and determining their symptoms and responses to treatment in order to try and refine medical practice. Some studies help researchers and clinicians determine whether dosing schedules, behavioral changes, and other elements of a treatment plan are realistic and appropriate. Clinical research sometimes overlaps with the category of epidemiological studies, which is described earlier in this chapter. These research studies can help researchers develop new interventions that can later be evaluated in clinical trials.

Generally, clinical trials, particularly those evaluating drugs or medical devices, are conducted in phases, each of which helps scientists answer different questions. In Phase I trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. Phase II trials involve a larger group of people (100-300) to evaluate the safety and

effectiveness of the study drug or treatment. In Phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely. Phase IV, or postmarketing, studies are conducted to gather information associated with long-term use in various populations.

The randomized clinical trial has long been considered the gold standard for evaluating the effectiveness of investigational treatments. "Randomization" means that subjects are assigned by chance to either the investigational intervention or the control group. The control group might include interventions such as usual care; best proven care; if known, or no treatment. The specific clinical trial design, including the types and number of intervention and control groups, is dependent upon the medical questions being posed. In addition to the use of control groups, clinical trials often use "blinded" or "masked" study designs, in which subjects are purposely not told whether they are in the intervention or the control group. If feasible, clinical trials are often "double-blinded" or "double-masked" so that the subjects as well as those conducting the study are unable to distinguish between the intervention and control groups.

Participation in clinical trials gives people an opportunity to contribute to the research effort and potentially gain early access to experimental treatments that might prove effective. For some research subjects, participating in a study can provide them with expert medical care at a leading health care facility. To help people access information about clinical trials for which they may be eligible, a Web site (http://www.clinicaltrials.gov) offers general information about clinical trials and provides a searchable database of specific studies around the world[9]. Research risks and potential benefits are carefully balanced and the burdens and benefits of participating are shared equally by appropriately including both sexes, people of all races/ethnicities (see Appendix E), and children. Balanced inclusion in trials allows investigators to know whether an intervention works equally well, or not, in all populations. NIH supports outreach efforts to recruit and retain children, women, minorities, and their subpopulations in clinical studies. In addition, NIH holds training events designed to help the research community better understand and be equipped to implement inclusion policy requirements. In 2006, in collaboration with FDA, NIH developed a Web-based course to create a strong foundation for implementation of the requirements for inclusion of minorities and women. The course addresses the scientific basis of known sex and gender differences and explores the influence of sex and gender differences on health outcomes and illness. Recognizing the importance of developing sound scientific bases for pediatric care while protecting children adequately in research settings, NIH policy requires that children (i.e., individuals younger than age 21) be included in human subjects research conducted or supported by the NIH, unless there are sound scientific and/or ethical reasons for excluding them.

In keeping with ethical mandates, NIH clinical research encompasses the principles of respect for persons, beneficence, and justice. Various NIH initiatives and programs seek to harmonize regulatory aspects governing the conduct of clinical research to ensure that studies are conducted with scientific rigor, with minimal burdens on research subjects and investigators, and with utmost consideration for the safety of subjects. In addition, NIH seeks to bolster participation in clinical trials by providing clinical trial educational materials, such as those targeted to cancer patients, health care professionals, and the general public to increase awareness of cancer clinical trials.

Fostering Collaborative NIH Clinical Research

NIH's efforts to bolster activities along the research continuum are enriching the pipeline of biomedical discoveries. To test investigational therapeutic and preventive strategies in the most expeditious way and hasten their entry into the clinic, NIH is supporting a wide variety of collaborations, research centers, and networks to conduct efficient clinical trials.

[9] As required by the NIH Reform Act of 2006, NIH provides an annual report to the U.S. Food and Drug Administration identifying all trials registered in www.clinicaltrials.gov.

Collaborations can consist of scientists at several institutions working together, or they may be intradepartmental or interagency government projects. As an example of such collaboration, NIH and the Centers for Medicare & Medicaid Services, which has an interest in developing an evidence base for Medicare coverage decisions,

[9]As required by the NIH Reform Act of 2006, NIH provides an annual report to the U.S. Food and Drug Administration identifying all trials registered in www.clinicaltrials.gov.

launched the largest ever randomized clinical trial of the effectiveness and safety of long-term home oxygen therapy for patients with chronic obstructive pulmonary disease.

NIH funnels the majority of its clinical trials funding to its extramural partners, which operate at the regional, State, and local levels. Many studies are conducted not just at one institution, but at many. Such multisite clinical trials help investigators quickly recruit enough subjects for studies; give the public the widest possible access to clinical studies; and address the special health concerns of high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. This approach was used in several practical clinical trials, the primary and secondary phases of which were recently completed. These studies examined treatment effectiveness for such mental disorders as schizophrenia, bipolar disorder, and depression, involving more than 10,000 subjects at more than 200 sites. The infrastructure developed for each of these trials forged collaborative relationships among scientists and clinicians around the country. The platform developed for the trials 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 future studies.

Large studies conducted at multiple sites often are best conducted through networks of investigators who are equipped with tools to facilitate collaboration and information sharing. NIH supports many clinical research networks by funding ongoing infrastructure that provides means of standardizing data reporting to enable seamless data- and sample-sharing across studies. Through NIH-funded informatics and other technologies, researchers are better able to broaden the scope of their research and avoid duplicating research efforts, thereby freeing time and funds to address additional research questions. Among the numerous networks established by NIH that have generated significant findings are the Maternal and Fetal Medicine Units Network, Neonatal Research Network, Obstetric Pharmacology Research Network, Collaborative Pediatric Critical Care Research Network, Pelvic Floor Disorders Network, Traumatic Brain Injury Clinical Trials Network, and Global Network for Women's and Children's Health Research. Additionally, the Community Cancer Centers Program, a 3-year pilot program to improve delivery of cancer care, builds upon the exemplary and long-lived Community Clinical Oncology Program, a network established in 1983 for conducting cancer prevention and treatment clinical trials. It has enrolled more than 200,000 people in treatment and prevention trials.

The Diabetic Retinopathy Clinical Research Network is a collaborative, nationwide public-private network of eye doctors and investigators at 165 clinical sites conducting clinical research on diabetes-induced retinal disorders with the aim of evaluating promising new therapies. This model network provides the infrastructure to facilitate clinical trials of innovative therapies, rapidly develop and initiate new protocols, and interact with industry partners while ensuring scientific rigor and high ethical standards.

Addressing Gaps in Research

In terms of clinical evaluation of drugs, there is no clear line where NIH work stops and the pharmaceutical industry picks up. Every drug candidate presents its own profile of financial risk and benefit and potential for gains in public health. NIH's aim is to be sure that all important leads are followed until they are mature enough to attract private-sector interest or until they reach a dead end. About half of the chemotherapeutic drugs currently used by oncologists for cancer treatment were discovered and/or developed by NIH. Cisplatin for treating testicular, ovarian, and lung cancer, and paclitaxel (Taxol) and fludarabine phosphate for treating several cancers and lymphoma, respectively, are examples where NIH involvement in early-stage drug development resulted in products that eventually were licensed to commercial organizations and reached the market. Recently, large-scale clinical trials of compounds that may prevent substance-abuse relapse demonstrated that the compounds were effective according to scientifically valid criteria accepted by FDA. If their efficacy is confirmed in NIH-sponsored

trials, these drugs will be the first generation of medications for treating stimulant dependence. In addition, NIH involvement has been central in developing effective interventions for diagnosis, management, or monitoring of HIV/AIDS, tuberculosis, arthritis, malaria, and many other conditions.

Because behavioral interventions generally do not involve marketable products or services, NIH has a special role to play in research on how changes in behavior can improve health. For example, the objective of Look AHEAD (Action for Health in Diabetes) is to examine cardiovascular outcomes in people with type 2 diabetes using the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. This multicenter, randomized clinical trial involves several ICs as well as the Centers for Disease Control and Prevention. A second example is the landmark NIH Diabetes Prevention Program clinical trial, which showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk for the disease. Researchers in a follow-on study found that study subjects benefited from healthy lifestyle changes regardless of their genetic disposition for developing the disease.

As noted earlier, government-funded research is particularly vital for the study of rare diseases. Not only do affected individuals benefit from new treatments that industry does not have the incentive to bring to market, but insights gained from such research often provide knowledge relevant to understanding more common diseases. For these reasons, NIH-funded investigators are studying an inherited retinal degenerative disease called Leber's congenital amaurosis (LCA), which causes severe vision loss in infancy or early childhood. Translational studies showed that vision could be restored in dogs with LCA using gene therapy to replace defective copies of the retinal gene RPE65. Phase I clinical trials of this type of gene therapy are now under way to determine whether this approach can help people with the condition.

Putting Clinical Research Results into Practice

Throughout this report are descriptions of important studies that are changing the way health care is practiced in this country, improving public health and enhancing well-being. To fully realize the potential of new interventions, research results must be disseminated and put into widespread use. NIH investigates strategies for adoption of new evidence at the community level, trains health care providers in best practices, carries out effectiveness research (head-to-head trials of known interventions), disseminates information to providers and the public based on the latest research findings, and sponsors research to learn about the most effective ways to disseminate such findings.

Changing Clinical Practice

It is not enough merely to have the infrastructure needed to address the ambitious goal of implementing science-based interventions and practices into community settings. In partnership with the Substance Abuse and Mental Health Services Administration and with researchers, clinicians, practitioners, and State alcohol and drug abuse directors, NIH is sharing strategies for incorporating research-based treatment findings into community settings. To accelerate the translation of research into practice in the case of addiction research, NIH embarked on the landmark Blending Initiative. This initiative takes what we know from science, identifies needed products, and disseminates them to providers of drug abuse and addiction treatment programs. The Blending Initiative also includes training components for addiction treatment practitioners.

The largest dataset ever assembled containing information about people with bipolar disorder has produced results with important implications for the way the condition is treated. NIH has taken important steps to ensure that findings from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) are translated into clinical practice. For the study, 4,360 individuals with bipolar disorder received best-practice treatments and were monitored throughout their participation in the study. As a critical translational step, participating doctors received expert training and became STEP-BD-certified in the best treatments for bipolar disorder. Among the consequential outcomes of the research was the finding that patients taking medications to treat bipolar disorder are more likely to get well faster and stay well if they also receive intensive psychotherapy.

NIH studies have transformed the management of antiretroviral therapy (ART) by directly comparing therapy regimens and determining which best extends survival of adults and children with HIV/AIDS. Results from the SMART study, one of the largest HIV/AIDS treatment trials ever conducted, showed that continuous ART is better than periodic therapy for treatment-experienced patients. Deliberately interrupting ART more than doubles the risk of developing AIDS or dying from any cause. The results of these studies stimulated immediate and significant changes in HIV treatment

Disseminating Research Findings

NIH is taking the lead in identifying the best ways to inform the public and health care practitioners about research results with the potential to improve the Nation's health (see the section on Health Communications in Chapter 3). For example, several large studies of type 1 and 2 diabetes established the importance of patients carefully maintaining blood-sugar control as a way to dramatically reduce the devastating complications of diabetes. Unfortunately, the therapies proven to delay or prevent complications in these studies are not widely incorporated into health care practice. Therefore, NIH is supporting projects exploring ways to disseminate knowledge from successful clinical research into medical practice and community settings. Many of these studies focus on minority populations disproportionately burdened by type 2 diabetes and obesity.

NIH continues to support research designed to strengthen the dissemination and implementation of evidence-based medicine. One example of many such initiatives is improving mental health practices by encouraging transdisciplinary teams to identify and overcome barriers to the adoption of evidence-based interventions. For example, a recent study reported that providing a minimal level of enhanced care for employees' depression would result in significant savings to employers.

NIH also promotes the fruits of its research by cataloging and disseminating data. For example, NIH leads the National Toxicology Program, an interagency initiative that produces the biennial *Report on Carcinogens*. Under this program, NIH staff members organize and publish data gleaned from numerous sources on some of the more than 80,000 chemicals registered for use in the United States. The 11th edition of the report identifies and discusses agents, mixtures, or exposure circumstances that could pose a health hazard because of carcinogenicity. It includes data on the carcinogenicity, genotoxicity, and biologic mechanisms of the listed substances in humans and/or animals; the potential for human exposure to these substances; and Federal regulations to limit exposures.

In its quest to help clinicians and patients make appropriate decisions about health care, NIH periodically convenes expert panels that review the cumulative research and publish clinical practice guidelines that describe a range of generally accepted approaches for the diagnosis, management, or prevention of specific diseases or conditions. The guidelines, which address such topics as asthma, cholesterol management, overweight and obesity, and HIV management, provide recommendations that patients and their doctors can use to develop individual treatment plans tailored to the specific needs and circumstances of the patient.

Located in the NIH Office of the Director, the Office of Medical Applications of Research (OMAR) works closely with ICs to assess, translate, and disseminate the results of biomedical research that can be used in the delivery of health services. OMAR coordinates periodic consensus conferences with the goal of reviewing areas of NIH-supported research where there may be a gap between research accomplishments and clinical care. The consensus statements that result from these conferences are shared widely with health care providers, policymakers, patients, and the media. Recent statements have addressed such topics as tobacco use, management of chronic insomnia, and multivitamin/mineral supplements.

Bolstering the Research Continuum

NIH is committed to reengineering the clinical research enterprise, a key objective of the NIH Roadmap for Medical Research. Three critical components of the Roadmap are capacity building, developing a multidisciplinary scientific

workforce dedicated to a new discipline of clinical and translational research to implement the Nation's research agenda, and harmonizing, streamlining, and optimizing policies and requirements concerning the conduct and oversight of clinical research.

Building Capacity for Clinical and Translational Research

NIH supports capacity building for clinical and translational research. Drawing on the momentum of the NIH Roadmap and extensive community input, the Clinical and Translational Science Award program is creating academic homes for the discipline of clinical and translational science at institutions across the country. Beginning with 12 academic health centers located throughout the Nation, the consortium will eventually link about 60 institutions. The program encourages the development of novel methods and approaches to clinical and translational research, enhances informatics and technology resources, and improves training and mentoring to ensure that new investigators can navigate the increasingly complex research system. The consortium of research institutions is radically changing how clinical and translational research is conducted and ultimately will enable researchers to provide new treatments more quickly to patients.

Researchers are increasingly conducting studies in community clinics, doctors' offices, and other health care facilities as innovative means of building capacity across the Nation and ensuring that diverse populations are involved in research. For example, NIH fosters scientifically rigorous research in oral health care in three networks of private dental practices to address the longstanding lack of high-quality research data to guide treatment decisions in the dentist's office. Each network is a grassroots effort, involving 100 or more community dentists and hygienists undertaking short-term clinical studies to compare the benefits of different dental procedures, dental materials, and prevention strategies.

Also, NIH is committed to expanding research capacity in the area of complementary and alternative medicine (CAM). By establishing various Centers of Research, both in the United States and abroad, based on collaborations between established biomedical research scientists and experts in CAM or traditional medicine, NIH has made significant advances in our understanding of the scientific basis for the effects of several CAM treatment approaches.

Developing the Research Teams of the Future

NIH is anticipating and preparing to meet the need for a multidisciplinary, well-trained cadre of researchers at every point in the research continuum through its career development initiatives (see section on Research Training in Chapter 3). For example, a key component of the CTSA program is the creation of one or more graduate degree-granting and postgraduate programs in clinical and translational science, which will provide an enriched environment for educating and retaining the next generation of clinical and translational researchers.

A Research Centers in **M**inority **I**nstitutions Translational Research **Net**work (RCMInet) will be a cooperative research network that will facilitate clinical research in health disparity areas. This Network will consist of a consortium of clinical investigators from the RCMI, RCMI Clinical Research Infrastructure Initiative (RCRII), and Clinical Research Education and Career Development (CRECD) programs; other NIH-supported Clinical Research Centers; relevant organizations, including community health centers, with an interest in health disparity areas; and a Data and Technology Coordinating Center (DTCC).

To respond to the identified need for more veterinarians in the field of biomedical research, NIH funds career development programs for veterinarians and veterinary studies, which are an important link between the use of animal models and their application to problems involving human health and disease.

Optimizing Policy

The NIH Clinical Research Policy Analysis and Coordination (CRpac) program serves as a focal point for the ongoing harmonization, streamlining, and optimization of policies and requirements concerning the conduct and oversight of clinical research. It is widely recognized that the efficiency and effectiveness of the clinical research enterprise is

hampered by variability in regulations and policies that pertain to the conduct and oversight of clinical research. The CRpac program reflects NIH's sense of responsibility, as the lead Federal agency supporting clinical research, to promote the efficiency and effectiveness of the clinical research enterprise by facilitating compliance and oversight. Its objective is to develop and implement coordinated policies and practices reflective of the needs and points of view of NIH's varied stakeholders. The CRpac program works on an array of issues and activities usually in close collaboration with other Federal agencies and offices that have responsibilities concerning the oversight of clinical research. CRpac's current focus includes issues related to Federal adverse event reporting requirements; clinical research review and oversight mechanisms; clinical trial monitoring; Federal regulations and policies governing research with human specimens and data; informed consent; and clinical trial design.

Conclusions

NIH's expanded commitment to optimizing the continuum spanning basic, translational, and clinical research by applying a new multidisciplinary approach to clinical and translational science marks a real turning point. Scientists will have more freedom to engage in productive collaborations with experts in different fields and follow creative approaches that will better serve human health as new treatments and prevention strategies are developed, tested, and brought more rapidly into practice. The results of NIH's commitment to clinical and translational science are apparent in the following section, which highlights a few of the myriad accomplishments and ongoing initiatives in this rapidly developing area of research.

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

Preclinical Research: Translating Basic Science Discoveries to Human Studies

Rodent Model Resources for Translational Research: Mouse and rat models are the primary testbed for preclinical research and have played a vital role in most medical advances in the last century. Rodent models comprise about 90 percent of all animal studies enabling a wide range of genetic and physiological research on human disease. NIH plays a major role in supporting the availability of normal and mutant mice and rats for translational research. Recent accomplishments include:

- Knockout Mouse Project (KOMP): A trans-NIH initiative to individually inactivate each protein-coding mouse gene to better understand the genetic functions of the estimated 22,000 mouse genes, which are, in many cases, very similar to human genes.
- KOMP Repository: Established in FY 2007 to acquire and distribute the mouse models produced by the KOMP.
- Mutant Mouse Regional Resource Centers: Distribution of genetically engineered mice increased by 50 percent in FY 2006 because of increased demand.
- Rat Resource and Research Center: Acquisition and distribution of rat models increased by 50 percent in FY 2006 because of increased demand.

    - For more information, see http://www.ncrr.nih.gov/comparative%5Fmedicine/resource_directory/rodents.asp
    - For more information, see http://www.genome.gov/17515708

- For more information, see http://www.genome.gov/25521840
- For more information, see http://www.mmrrc.org/
- For more information, see http://www.nrrrc.missouri.edu/
- This example also appears in Chapter 3: *Genomics*.
- (E) (NCRR)

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 (FXS): NIH has entered into a public-private partnership to study and test possible medications for treating FXS, the most common cause of inherited mental impairment. FXS is caused by a single gene mutation, ultimately resulting in exaggerated activity of a brain protein called mGluR5. Researchers will study, in animals, the safety of chemical compounds known to block 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 persons with treatment-resistant depression experienced relief in as little as 2 hours following 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 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*.
    - (I) (NIMH)

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 as a result of 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 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCR)

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 individual's disease or tumor so that tailored medical strategies can be applied. 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/profiles derived from molecular analysis of tumors (i.e., biomarkers detection) to improve patient management and outcomes.

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

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 only from 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 using magnetic resonance imaging (MRI). They label macrophages (immune cells) with polymer-coated micron-size 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 the present time 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 2: *Chronic Diseases and Organ Systems*.
  - (E) (NIBIB)

Basic Research on CAM: In addition to its focus on clinical investigation of complementary and alternative medicine interventions, NIH places a high priority on basic research aimed at filling important gaps in our knowledge about the mechanisms by which they may exert their effects. Recently released initiatives target this area of research. Examples include the following:

- "Omics and Variable Responses to CAM" utilizes genomic, proteomic, and metabolomic technologies to examine potential causes for variation in individual responses to CAM interventions (PAR-07-377).
- "Mechanistic Research on CAM Modalities Purported to Enhance Immune Function" examines the scientific basis for a common but generally unsubstantiated claim made on behalf of a number of CAM modalities (RFA-AT-06-004, RFA-AT-06-005).
- "Research on the Biomechanical, Immunological, Endocrinological, and/or Neurophysiological Mechanisms and Consequences of Manual Therapies" applies state-of-the-art science to investigate the biological basis for CAM interventions, such as spinal manipulation and massage. (PAR-06-312)

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

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 2: *Cancer*.
- (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, visit http://nano.cancer.gov/
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Technology Development*.
- (E/I) (NCI)

Biomedical Technology Research Resources (BTRRs): The BTRRs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Resources and through intensive collaborations with other leading laboratories. The BTRRs are used annually by nearly 5,000 scientists from across the United States and beyond, representing over $700 million of NIH funding for 22 institutes and centers. As an example, optical technologies enable researchers to:

- Harness the power of light to "see" biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.
- Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margins of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

- For more information, see www.ncrr.nih.gov/biomedical_technology
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*
- (E) (NCRR)

Glycomics Technology Development, Basic Research, and Translation into the Clinic: Complex carbohydrates are ubiquitous, found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules are thus critical for basic and clinical research across the spectrum of health and disease but are widely regarded as among the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- Biomedical Technology Research Resources are developing and sharing cutting-edge technologies for analysis of carbohydrates in complex biological systems.
- Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.

- Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.
- A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.

    - For more information, see www.ncrr.nih.gov/glycomics
    - For more information, see www.functionalglycomics.org
    - This example also appears in *Chapter 3: Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
    - (E) (**NCRR**, NCI, NHLBI, NIGMS, NINDS)

Preclinical Disease Models Informatics: Preclinical research results derived from animal models are an essential element in the decisional process to determine whether a basic science discovery should be considered as a potential therapeutic approach worthy of future development. However, more effective integration of the growing number of disparate data sources is urgently needed. NIH is developing a new resource to assimilate information from diverse disease-model data repositories and to disseminate innovative and novel interpretations of these data. This will help researchers minimize the time required to search multiple data sources, while optimizing the quality and relevance of the results. Activities in this area include:

- Determined community-defined needs and next steps during a workshop held in FY 2006.
- Issued request for proposals (fall 2007) that will address the need for an electronic directory of models resources.
- Forming critical inter/intra-agency and public-private partnerships to (1) address the need for and development of extensible prototypes and (2) ensure this resource remains broadly informed and grows coincidental with relevant technology.

    - For more information, see www.esi-bethesda.com/ncrrworkshops/navigating/index.aspx
    - (E) (NCRR)

Translational Research at Primate Research Centers: Non-human primates (NHPs) are critical components for translational research because of their close physiological similarities to humans. NHPs 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 NHPs. In FY 2007, more than 1,000 research projects used NHPs 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 FY 2006 and 2007 that further defined the genetic tools necessary for translational research using NHPs.

    - For more information, see ncrr.nih.gov/comparative%5Fmedicine/resource_directory/primates.asp
    - This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
    - (E) (NCRR)

Medical Countermeasures Against Nuclear and Radiological Threats: NIH is leading the HHS effort to sponsor and coordinate research to develop means to counter 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 2: *Infectious Diseases and Biodefense*.
- (E) (NIAID)

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 2: *Minority Health and Health Disparities*.
- (E) (NIAMS)

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 and lead to the first true treatment for stroke, one of the most common causes of disability, severely affecting 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIBIB)

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 Genetic Association Information Network (GAIN), a public-private partnership between NIH and industry.

- 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
- (E) (NIDDK)

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 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, prepared and tested by T1D-RAID, 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 2: *Autoimmune Diseases*.
- (E) (**NIDDK**, NCI)

Specialized Program of Translational Research in Acute Stroke (SPOTRIAS): The objective of the SPOTRIAS is to serve as an incubator for translational and early-phase clinical research studies. SPOTRIAS sites are located at medical centers where staff members 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (COE) (**NINDS**, NIAMS, NICHD) (GPRA Goal)

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 causing SMA dramatically improved prospects, revealing a rational strategy to develop drugs. The SMA Project is a novel approach to pre-clinical drug development and may serve as a model for other disorders. The Project 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 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NINDS)

Translational Research: To meet the special needs of translational research across neurological disorders, NINDS 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, with expertise and criteria 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NINDS)

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 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. The NIH-RAID Pilot 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (Roadmap—all ICs participate)

Translational Research on Alzheimer's Disease (AD): To move basic research on AD and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. In order 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 held 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 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NIA)

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 pre-teen 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 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 2: *Life Stages, Human Development, and Rehabilitation*.
- (I) (NHGRI)

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 2: *Autoimmune Diseases*
- (I) (NHLBI, NIAID, NIAMS, NIDDK)

Clinical Research: Learning Which Interventions Work

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 man-made reversible adhesive. It is envisioned that the new adhesive will be used for many medical applications including enhancing the retention of oral/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 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*.
- (E) (NIDCR)

Diabetes Prevention Program Outcomes Study (DPPOS): The landmark NIH Diabetes Prevention Program clinical

trial showed that lifestyle change or treatment with the drug metformin significantly delayed development of type 2 diabetes in people at high risk. The DPPOS is a long-term followup study of the 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, as 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) while 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (**NIDDK**, CDC, IHS, NCMHD, NEI, NHLBI, NIA, NICHD, ORWH)

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 while 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NINDS)

Multiple Sclerosis (MS): While the exact cause of MS is unknown, research suggests a strong genetic component. NIH funds a number of studies to determine the underlying genetic causes of MS, including a project to identify regions of the genome containing MS susceptibility genes using a large familial dataset and genomic analysis tools. NIH also funds clinical trials to test therapies for MS, including the CombiRx trial, a randomized, controlled clinical trial comparing the efficacy of treatment combining interferon-beta (IFN) and glatiramer acetate (GA) 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 MS biomarkers 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 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (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 MD: one to develop small molecule drugs for Duchenne and potentially other forms of MD and another to develop the optimal vector for vascular delivery of genes. A new NIH GPRA goal aims to advance two emerging strategies for treating MD to clinical trial readiness by 2013. The Muscular Dystrophy Coordinating Committee's (MDCC) *Action Plan for the Muscular Dystrophies* also identified therapy development goals to be pursued by NIH and its MDCC partner agencies and organizations. A recent workshop convened by NIH reviewed the status of different therapeutic approaches for MD 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 2: *Neuroscience and Disorders of the Nervous System*
- (E) (**NINDS**, NIAMS, NICHD)

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 multi site trials—involving over 10,000 subjects at over 200 sites—has forged efficient, effective, and collaborative relationships between scientists and clinicians throughout the country. In order 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 between 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: *Neuroscience and Disorders of the Nervous System* and Chapter 2: Chronic Diseases and Organ Systems
- (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 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 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 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 2: *Neuroscience and Disorders of the Nervous System*.
- (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 contribute 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 2: *Neuroscience and Disorders of the Nervous System*
- (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 and early childhood. Although currently untreatable, NIH-funded investigators have restored vision in dogs with LCA 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 2: *Chronic Diseases and Organ Systems*.
- (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 often requiring 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 severe uveitis.

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

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 sickle cell disease patients who have pulmonary hypertension. A randomized, double-blind, placebo-controlled Phase II clinical trial is testing the drug's safety and its 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: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E/I) (NHLBI)

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.htm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.

- (E) (NIDCR)

The PCOS Twin Study: The PCOS (Polycystic Ovarian Syndrome) Twin Study is sponsored by NIH. NIH researchers are studying polycystic ovary syndrome in twins to find out if it is caused by genetics or the environment or a combination of both. Once scientists know more about the causes of PCOS, then health care professionals can then treat it more effectively or possibly lower the chance that a woman will develop it.

- For more information, see http://www.niehs.nih.gov/pcos/index.htm
- (I) (NIEHS)

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. While radiation therapy kills cancerous cells, it frequently also destroys the acinar (fluid-producing) salivary gland cells that lie within the salivary gland in grape-like 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. But 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 2: *Cancer*.
- (I) (NIDCR)

Long-Term Oxygen Treatment Trial (LOTT): Although oxygen therapy is known to benefit patients who have chronic obstructive pulmonary disease (COPD) and experience severe hypoxemia (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 management of such patients and to provide a basis for Medicare coverage decisions. LOTT is the focus of a new NIH Government Performance and Results Act (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.nhlbi.nih.gov/new/press/06-11-20.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*
- (E) (NHLBI) (GPRA Goal)

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/news/newsreleases/2007/ctu07.htm
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NIAID) (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 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E/I) (**NIDDK**, CDC, NCMHD, NHLBI, NINR, ORWH) (GPRA Goal)

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 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIMH)

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 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 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (**NEI**, NIA)

Improved Management of Antiretroviral Therapy for Adults and Children: Two recent NIH studies transformed the management of antiretroviral therapy (ART) by extending 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 ART based on CD4+ cell levels is inferior to 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 ART in South African children. Interim data showed a 96 percent increase in survival among infants who received immediate ART compared to 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 2: *Infectious Diseases and Biodefense*.
- (E) (NIAID)

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 under three. 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.

- For more information see http://www3.niaid.nih.gov/topics/allergicDiseades/researchActivities.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIAID)

Therapies to Treat and Prevent Food Allergies: The NIH Consortium of Food Allergy Research is developing immune-based approaches to treat food allergy, rather than to simply avoid food allergens. Basic studies are ongoing using mouse models to study how modified forms of peanut allergens protect against peanut-induced anaphylaxis. The five clinical sites of the Consortium are developing treatment and prevention strategies for food allergy, and they work to educate parents and health care providers regarding food allergies. An ongoing observational study is examining immune mechanisms, genetic factors, and environmental factors associated with the development of new food allergy to peanut and the loss of egg allergy to high-risk children. An interventional study aims to determine the safety and immunologic effects of giving egg by mouth to egg-allergic children, with the goal of inducing immunological tolerance. Phase I clinical trials are assessing the safety of treating peanut-allergic subjects with either a modified form of peanut allergen or small amounts of peanut allergen under the tongue.

- For more information, see http://www3.niaid.nih.gov/topics/foodAllergy/default.htm
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIAID)

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 joint and muscle (TMJ) 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 TMJ 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 http://www.nidcr.nih.gov/Research/ResearchResults/InterviewsOHR/TIS012006.htm
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDCR)

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 additionally 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: *Chronic Diseases and Organ Systems* and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (**NIDDK**, ORWH)

Polycystic Kidney Disease (PKD): The Consortium for Radiologic Imaging Studies of PKD (CRISP) showed that magnetic resonance imaging could accurately track structural changes in the kidneys in 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 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 2: *Chronic Diseases and Organ Systems* 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 2: *Chronic Diseases and Organ Systems*.
- (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 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*, Chapter 3: *Epidemiological and Longitudinal Studies*, and Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (**NIDDK**, CDC)

Centers on Suicide Prevention: In response to the 2002 Institute of Medicine Report, "Reducing Suicide: A National Imperative," NIH issued a request for applications and funded three centers focused on intervention and prevention of suicide. 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (**NIMH**, NIAAA, NIDA)

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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH)

ClinicalTrials.gov: Established in 2000 in response to congressional mandate (Pub. L. No. 105-115), ClinicalTrials.gov has grown to become the largest clinical trial registry in the world with information on clinical research studies for hundreds of diseases and conditions conducted in 148 countries. At the end of September 2007, it contained more than 47,000 registered trials—more than double the number of entries 2 years earlier. Legislation enacted in September 2007, the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85), expanded the scope of trials to be registered with ClinicalTrials.gov and the registration information to be provided. It also mandates the inclusion of specified results information beginning in September 2008.

- Drazen JM, et al. *N Engl J Med* 2007;356:184-5, PMID: 17215537
- Zarin DA, et al. *N Engl J Med* 2005;353:2779-87, PMID: 16382064
- For more information, see http://clinicaltrials.gov
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (I) (NLM)

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: *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NCCAM)

Research on Popular Dietary Supplements: A significant body of research on complementary and alternative medical 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 1200 IU/day for 2 years had no effect on serum concentrations of total, LDL, or HDL cholesterol.

- Clegg DO, et al. *N Engl J Med* 2006354:795-808, PMID: 16495392
- Singh U, et al. *Clin Chem* 2007;53:525-8, PMID: 17234730
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHLBI)

Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial: The HALT-C trial studies whether long-term antiviral therapy can prevent liver disease progression 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 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 2: *Chronic Diseases and Organ Systems*
- (E) (**NIDDK**, NCI, NIAID)

Compliance With the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research: NIH works to ensure compliance with the NIH Policy for the Inclusion of Women and Minorities as Subjects in Clinical Research by convening a trans-NIH committee that addresses consistency in inclusion policy implementation and population data reporting. Over the last 2 years, a more streamlined method of reporting minority participation in

NIH-funded clinical research has been developed; the most recent Federal standards for reporting race and ethnicity have been clarified; and new methodologies for collecting and reporting more reliable population data from investigators have been implemented. In 2007, ORWH collaborated with OER in providing training sessions for grants management, review, and program staff on implementation of the NIH inclusion policy. These mandatory training sessions, "Sex/Gender, Race and Ethnicity Inclusion in Clinical Research," were designed to help participants better understand congressionally mandated inclusion policies and how to implement them, reemphasized the vital role and responsibilities of NIH staff members in the management of grants, contracts, and cooperative agreements that involve human subjects research, and also highlighted the role of NIH staff, peer reviewers, and investigators in meeting inclusion policy requirements. In addition to these activities, NIH prepared the annual aggregate comprehensive reports: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research (see Appendix E) as well as the 2007 Biennial Report Certifying IC Compliance with the Inclusion Guidelines based upon IC Advisory Council reviews, as required by statute.

- For more information, see http://orwh.od.nih.gov/inclusion.html
- (E, I) (**ORWH**, OER)

Developing Pediatric Drug Data: Clinicians prescribing pharmaceuticals for sick infants nd children face major gaps in the scientific data on safety and efficacy of pharmaceuticals for their young patients. Obtaining available data from drug trials in adults is often problematic because of important differences in the ways that drugs act in the bodies of adults and children. Furthermore, data from adults cannot be used to characterize the effects of drugs on children's development and health over time. To respond to this concern, Congress passed the Best Pharmaceuticals for Children Act (BPCA) to support the additional research needed to test the effect of pharmaceuticals specifically for children. NIH, in collaboration with FDA and private-sector experts and organizations, maintains an extensive program for identifying priority drugs used "off label" in children—that is, prescribed without safety and efficacy data that would be required for FDA to approve or label them for use in children. This program involves requests to industry for needed pediatric research on priority "off-patent" drugs and conducting studies of priority drugs that industry declines to undertake. Under NICHD leadership, NIH Institutes participate in the ongoing BPCA program, including its funding.

- For more information, see http://bpca.nichd.nih.gov/index.cfm
- (E/I) (NICHD)

Web-Based Instruction on the Science of Sex and Gender in Human Health: NIH, in collaboration with the Office of Women's Health, U.S. Food and Drug Administration (FDA), developed a Web-based course in 2006 to create a permanent foundation for sex and gender accountability in medical research and treatment. The course provides uniform instruction for physicians and scientists to meet the NIH and FDA requirements for inclusion, and the implications of sex and gender differences for policy, research, and health care. The course addresses the scientific basis of known sex and gender differences and explores the influence of sex and gender differences on health outcomes and illness. Each lesson is interactive and includes seminal references on topics such as developmental biology and pharmacogenomics.

- For more information see http://sexandgendercourse.od.nih.gov/
- (E) **ORWH**, NICHD, NHLBI, FDA, AHRQ

Putting Clinical Research Results Into Practice

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. 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, 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, Schottenfeld RS, Chawarski MC. *Drug Alcohol Rev* 2006;25:473-8, PMID: 16939945
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (**NIDA**, NIAID)

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 ~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 the Centers for Disease Control and Prevention (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 Chapter 2: *Infectious Diseases and Biodefense* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NIDA)

Diagnostic Genetic Test Translation From the Research Laboratory to the Clinic: Because the majority of rare diseases are genetic disorders, genetic testing is an essential part of diagnosis and treatment. Few incentives exist for translating research findings into clinical tests that are available to the public. To address this gap, NIH created the Collaboration, Education and Test Translation (CETT) for Rare Genetic Diseases pilot program. The CETT pilot program brings new genetic and diagnostic tests to patients, encourages clinical laboratory and research collaborations, and stimulates dialogue with patient advocacy groups. Goals include developing models for information on clinical uses of the test; how the test results will be interpreted for clinical care providers, patients, and their families; methods to collect and store in publicly accessible databases the clinical information on each sample necessary to interpretation, while at the same time respecting confidentiality; and methods to collect and store test result information in publicly accessible databases. Since February/March 2006, 21 tests have been reviewed and 19 have been approved. The CETT pilot program has seen the successful development of 10 clinical tests for Cornelia de Lange syndrome, Joubert syndrome, cherubism, X-linked chondrodysplasia punctata, Kallmann syndrome, progressive familial intrahepatic cholestasis, Russell Silver syndrome, MPS VI, Niemann Pick disease A/B, and X-linked periventricular nodular heterotopia. These tests address more than 18 conditions and 13 genes. Tests for primary ciliary dyskinesia, infantile neuroaxonal dystrophy, and arginase deficiency will be

released later this year and more tests are under development.

- For more information, see http://www.cettprogram.org
- (E/I) (**ODP/ORD**, NLM)

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. Remove the light, and 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, while 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 2: *Cancer* and Chapter 3: *Technology Development*.
- (E) (NIDCR)

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 NCMHD and others cofunds the HEAL Project (Head Off Environmental Asthma in Louisiana) to assess the impact on asthma in New Orleans children of environmental health conditions that were caused and exacerbated by Hurricane Katrina, as well as to implement an intervention program to address these problems. The project's three main goals are to conduct an extensive epidemiology study to assess the nature of the environmental and psychological impacts of Hurricane Katrina and subsequent flooding on children in New Orleans; to examine the genetic and environmental risk factors for asthma, including genetic susceptibility to mold toxins, and gene interactions; and 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 2: *Minority Health and Health Disparities*
- (I) (NIEHS, NCMHD)

The Report on Carcinogens, Eleventh Edition: More than 80,000 chemicals are registered for use in the United States. Each year, an estimated 2,000 new ones are introduced for use in such everyday items as foods, personal care products, prescription drugs, and household cleaners. In response to concerns about the relationship between environment and cancer, the National Toxicology Program (NTP), an interagency program led by NIEHS, produces the Report on Carcinogens (RoC) biennially. The RoC is an informational scientific and public health document that identifies and discusses agents, mixtures, or exposure circumstances that may pose a hazard to health by virtue of their carcinogenicity. It includes data on the carcinogenicity, genotoxicity, and biologic mechanisms of the listed substances in humans and/or animals, the potential for human exposure to these substances, and Federal regulations to limit exposures.

- For more information, see http://ntp.niehs.nih.gov/files/11thROC_factsheet_1-31-05.pdf
- For more information, see http://ntp.niehs.nih.gov/go/roc

- (O) (NIEHS)

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 trained to implement them. This work is occurring through the National Drug Abuse Treatment Clinical Trials Network (CTN) at NIH, which involves practitioners from community treatment programs (CTPs) 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 CTPs 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: *Chronic Diseases and Organ Systems*, Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*, and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (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, etc. and (2) Motivational Incentives for Enhanced Drug Abuse Recovery, a cost-effective incentive method for cocaine and methamphetamine addiction, 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: *Chronic Diseases and Organ Systems* and Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIDA)

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 (PAR) to encourage transdisciplinary teams of scientists and practice stakeholders to work together to develop innovative approaches for identifying and overcoming barriers to the adoption of evidence-based interventions. This PAR serves as the basis for a GPRA Goal as well. 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
- (E/I) (**NIMH**, NCI, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NINR) (GPRA Goal)

Science of Dissemination and Implementation: Relatively little is known about how to ensure that the lessons learned from research inform and improve the quality of health and human services in the population at large. The goals of the program announcement, *Dissemination and Implementation Research in Health, and conference, Building the Science of Dissemination and Implementation in the Service of Public Health* (September 2007), are to support innovative approaches to identifying, understanding, and overcoming barriers to the adoption, adaptation, implementation, and maintenance of evidence-based practices by health providers, insurers, policymakers, and the public.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-086.html
- For more information, see http://obssr.od.nih.gov/di2007/index.html
- This example also appears in Chapter 3: *Health Communication and Information Campaigns* and *Clearinghouses*.
- (E) (**NCI**, NHLBI, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIMH, NINR, OBSSR, ODS)

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 2: *Minority Health and Health Disparities*.
- (E) (NIDDK)

Comprehensive Review of Meditation Research: A recent comprehensive literature review on meditation research included over 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 2: *Chronic Diseases and Organ Systems*.
- (E) (NCCAM)

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 likely 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 2: *Chronic Diseases and Organ Systems*.
- (E) (**NIAMS**, NIOSH, ORWH)

Neonatal Onset Multisystem Inflammatory Disease (NOMID): For children and young adults who suffer from a rare and debilitating disorder called NOMID, the arthritis drug anakinra brings marked improvement in both symptoms and the inflammation underlying the disease.

- Goldbach-Mansky R, et al. *Arthritis Rheum* 2007;56:2099-101; author reply 2101-2, PMID: 17530657
- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2006/08_09.asp
- (I) (NIAMS)

Bolstering the Research Continuum

Clinical Trials Education: Materials 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://cancer.gov/publications
- This example also appears in Chapter 2: *Cancer* 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: 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 over 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, for example, CRN research documenting specific gaps in implementing effective tobacco cessation services among clinicians, reasons for late diagnosis of breast and cervical cancer, more rapid uptake in the use of aromatase inhibitors in comparison to 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 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 identified that although biopsy rates are twice as high in the United States in comparison to the United Kingdom, cancer detection rates are very similar in the two countries.

- In an effort to address 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, the **Cancer Care and Outcomes Research Surveillance Consortium (CanCORS)** was established. It 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 2: *Cancer*, Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*, and Chapter 3: *Epidemiological and Longitudinal Studies*.
    - (I) (NCI)

Clinical and Translational Science Award (CTSA) Program Progress: Since the inception of the CTSA program, NIH has made significant progress in building a national consortium for clinical and translational research. The first CTSA awards were made in September 2006 to 12 academic health centers (AHCs) throughout the country, along with 52 planning grants to help institutions prepare to join the Consortium in the future. To meet the goal of 60 CTSA sites by 2012, NIH has developed and released annual funding opportunity announcements, which will provide AHCs, including those with General Clinical Research Centers (GCRCs), an opportunity to build on their existing resources and transform into this new integrated program. The CTSA infrastructure will not only enhance the research capacity already developed through the GCRC program, but will also create an integrated home for clinical and translational research and training. During the transition to the CTSA program, NIH is continuing to work closely with GCRCs and is allowing them flexibility on a case-by-case basis to plan and apply for a CTSA award.

- For more information, see http://www.ctsaweb.org/
- (E) (NCRR)

Clinical Research Networks: Clinical research is essential for translating laboratory findings into evidence-based interventions targeting an array of public health concerns. Many research programs involve collaborative networks, drawing scientists together to bring the benefits of clinical research to high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. Among such networks that have generated significant findings to advance medical practice and improve public health are the Maternal and Fetal Medicine Network, Neonatal Research Network, Obstetric Pharmacology Research Network, Pediatric Critical Care Research Network, Pelvic Floor Disorders Network, Traumatic Brain Injury Clinical Trials Network, and Global Network for Women's and Children's Health Research.

- For more information, see http://www.bsc.gwu.edu/mfmu/, https://neonatal.rti.org
- For more information, see http://www.nichd.nih.gov/about/org/crmc/opp/index.cfm
- For more information, see http://www.cpccrn.org/, http://www.pfdnetwork.org/
- For more information, see http://www.nichd.nih.gov/research/supported/TBI.cfm
- For more information, see http://www.nichd.nih.gov/publications/pubs/upload/GlobalNetwork.pdf
- (E) (**NICHD**, FIC, NCCAM, NCI, NIDCR, NIDDK, ORWH)

Centers of Excellence for Research on CAM (CERC), Developmental Centers for Research on CAM (DCRCs), and International Centers for Research on CAM: These Centers bring cutting-edge scientific technology to programs of research on the usefulness, safety, and mechanisms of action of various CAM interventions. Based in collaborations between established biomedical research scientists and experts in CAM or traditional medicine, these programs are also aimed at enhancing the global state of research capacity on CAM. For example, the CERCs are led by scientists with outstanding research records who direct teams of investigators with both CAM and conventional scientific expertise. During the first 3 years of the CERC program, awardees have made sentinel

advances in our understanding of the scientific basis for the effects of acupuncture through the use of modern brain imaging, and they have explored innovative approaches to the treatment of asthma with antioxidants and approaches based on traditional Chinese medicine (TCM). Other CERCs are focusing on (1) the study of acupuncture and TCM herbal treatments of arthritis, (2) the effects of mindfulness meditation on the progression of HIV/AIDS, and (3) the mechanisms of action of millimeter wave therapy (use of low-intensity millimeter wavelength electromagnetic waves) for a variety of chronic conditions. NIH will fund additional CERCs in late FY 2007.

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

Resuscitation Outcomes Consortium: Recognizing the critical importance of early intervention for victims of cardiopulmonary arrest and traumatic injury, in FY 2004 NIH and its U.S. and Canadian partners initiated the Resuscitation Outcomes Consortium, a large-scale network to conduct clinical trials of promising approaches to improving outcomes. During FY 2006-2007, two Consortium clinical trials began enrolling patients—one to compare the efficacy of three fluids for initial resuscitation of hypotensive or brain-injured patients, and the other to test two strategies for increasing blood flow during cardiopulmonary resuscitation. The Consortium also established a pre-hospital Cardiac Arrest and Trauma Registry across the United States and Canada. In addition, emergency medicine fellowship training programs established at several study sites are enhancing training in resuscitation medicine.

- For more information, see https://roc.uwctc.org/
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (**NHLBI**, NINDS)

Alzheimer's Disease Cooperative Study (ADCS): Much of the AD-related clinical research supported by NIH takes place through the ADCS. The study involves a consortium of centers in the United States and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of AD 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 (IVIg) is clinically useful for treating AD and a trial to examine whether treatment with docosahexaenoic acid (DHA), an omega-3 fatty acid, will slow cognitive decline in patients with AD.

- For more information, see http://www.nia.nih.gov/NewsandEvents/PressReleases/PR20061017ADCS.htm
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIA)

The Immune Tolerance Network: In 2007, NIH renewed support for the Immune Tolerance Network (ITN), a consortium of over 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 “reeducate” 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 to current methods that require years of biweekly injections. Current ITN studies include pancreatic islet transplantation for type 1 diabetes; approaches to slow or reverse 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 2: *Autoimmune Diseases* and Chapter 3: *Molecular Biology and Basic Sciences*
- (E) (NIAID)

A Multidisciplinary Approach to Nicotine Addiction: Nicotine addiction is the number one preventable public health threat, with 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 associated with nicotine addiction that could provide new targets for medications 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 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 ever 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 3: *Genomics*, Chapter 2: *Cancer,* and Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (**NIDA**, NCI) (GPRA Goal)

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 the 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (**NHLBI**, NIAID) (GPRA Goal)

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 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NIAAA) (GPRA Goal)

Antimicrobial Resistance Research: Antimicrobial resistance, caused by factors such as overuse of antibiotics, is severely jeopardizing the utility of many "first line" antimicrobials 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. For example, clinical studies are testing interventions for community-acquired multidrug-resistant Staphylococcus aureus (CA-MRSA) infection and to evaluate the efficacy of off-patent antimicrobials. A clinical study is evaluating the efficacy of antimicrobials in young children with acute ear infections through the comparison of symptom resolution in children receiving antimicrobial therapy versus placebo. Research initiatives such as "Sepsis and CAP [Community-Acquired Pneumonia]: Partnerships for Diagnostics Development" and "Partnerships to Improve Diagnosis and Treatment of Selected Drug-Resistant Healthcare-Associated Infections" are supporting the development of new diagnostics to facilitate the optimization of antimicrobial therapy and eliminate the overuse of broad-spectrum antimicrobials. 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://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm.
- For more information, see http://www3.niaid.nih.gov/topics/AntimicrobialResistance/research/default.htm
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E/I) (NIAID) (GPRA Goal)

Improving Transplantation Outcomes: Organ transplantation prolongs survival and improves quality of life for children and adults suffering from 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 2: *Chronic Diseases and Organ Systems*.
- (E) (**NIAID**, NHLBI) (GPRA Goal)

Clinical, Operational, and Health Services Research Training (noncommunicable diseases): To successfully develop and implement health interventions in the developing world, a well-trained cadre of scientists is needed to plan, design, and conduct clinical, operational, health services, and prevention science investigations. NIH funds research training in these disciplines, which supports the development and implementation of evidence-based interventions for non-communicable disorders/diseases in low- to middle-income countries. Projects funded by this program require collaboration between U.S. and foreign institutions and include epidemiology, health services, and genetics research on major psychiatric disorders in India; a study examining the impact of institutionalization on children in Turkey; and multidisciplinary training in substance abuse research in Eastern Europe.

- For more information, see http://www.fic.nih.gov/programs/training_grants/icohrta/index.htm
- This example also appears in Chapter 3: *Research Training and Career Development*.

- (E) (**FIC**, NIA, NIDA, NIDCR, NIMH, NINDS, ODS)

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 who 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: *Research Training and Career Development* and Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (FIC, NCI, NIAID, NHLBI, NIDA, NIDCR, NIMH, NINDS, NINR, OAR, ORWH)

Clinical Trials Networks: These 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, over 200,000 people have enrolled in treatment and prevention trials. An example is the Study of Tamoxifen and Raloxifene trial (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.
- 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 non-small cell lung cancer (NSCLC), their overall survival, progression-free survival, and response rates significantly increased.
- 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, see http://www.cancer.gov/STAR
- For more information, see http://dcp.cancer.gov/programs-resources/programs/ccop
- For more information, see http://ctep.cancer.gov/
- For more information, see http://ncccp.cancer.gov/
- This example also appears in Chapter 2: *Cancer*.
- (E) (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,

as well as novel combinations of chemotherapy with concomitant boost radiation therapy, in non-small cell lung cancer.

- 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 2: *Cancer*.
- (I) (NCI)

The NCI Vaccine Program: The 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 to potentially save over 5,000 U.S. women's lives each year. This FDA-approved vaccine resulted from the basic research performed at NIH producing a prototype vaccine and the observation that linked the human papillomavirus (HPV) and cervical cancer.

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

Career Development for Veterinarians in Translational Biomedical Research: Two recent reports from the National Academies, *National Need and Priorities for Veterinarians in Biomedical Research and Critical Needs for Research in Veterinary Science*, have confirmed the shortage of veterinarians involved in biomedical research. To address the shortage, NIH provides career development awards in biomedical research specifically for veterinarians and veterinary students. Mentored Career Development Awards to veterinarians serve as a bridge for postdoctoral fellows to become independent investigators. In FY 2006, 25 career development awards were made to young veterinary investigators to increase the number of researchers in this field. Additionally, an initiative that began in FY 2007 encourages the specialization of veterinarians in clinical medicine at NIH-supported primate centers to address the shortage of clinical veterinary support for research primate colonies.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-RR-06-006.html
- For more information, see http://www.ncrr.nih.gov/career_development_opportunities/individual_training_grants/
- National Need and Priorities for Veterinarians in Biomedical Research: http://books.nap.edu/catalog.php?record_id=10878
- Critical Needs for Research in Veterinary Science: http://books.nap.edu/catalog.php?record_id=11366
- (E) (NCRR)

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)

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 statewide collaborative partnerships that increase institutions' capacity to conduct cutting-edge biomedical research. IDeA supports faculty development and enhancement of research infrastructure at institutions and also promotes collaborative community-based research, particularly in minority communities and other medically underserved communities where health disparities persist. The IDeA program supports the IDeANet initiative, which is expanding access to high-performance computational resources for data-intensive science applications and providing bioinformatics software tools and training to investigators. IDeANet began with 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 participants 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 2: *Minority Health and Health Disparities*.
- (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 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 http://www.ncrr.nih.gov/research_infrastructure/research_centers_in_minority_institutions/
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (**NCRR**, NCMHD, NHLBI, NIA, NIAID, NIAMS, NICHD, NIDA, NIDDK, NIMH)

Shared Instrumentation Grant and High-End Instrumentation Programs: The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the $100,000-$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the $750,000-$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located on core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational research. In FY 2006 and 2007 the SIG program funded a total of 264 grants for $95.2 million; the HEI funded a total of 39 awards for $55.9 million.

- For more information, see http://www.ncrr.nih.gov/biomedical_technology/shared_instrumentation/
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NCRR)

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, 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 2: *Chronic Diseases and Organ Systems*.
- (E) (NEI)

Retinal Neurodegeneration Program: This new multidisciplinary intramural research program 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 2: *Neuroscience and Disorders of the Nervous System*.
- (I) (NEI)

Multiplex Initiative: With the completion of sequencing 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 followup 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (I) (NHGRI)

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 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: *Chronic Diseases and Organ Systems* and Chapter 2: *Minority Health and Health Disparities*.
- (E) (NHLBI)

Dental Practice-Based Research Networks: NIH has established three regional dental practice-based research networks (PBRNs) to perform clinical research in areas that are not well suited for the academic or laboratory setting. Each PBRN involves 100 or more research-trained dentists and dental hygienists who will propose and conduct studies across a range of patient and clinical conditions. The PBRNs also will collect information to generate data on disease, treatment trends, and the prevalence of less common oral conditions. The success of the PBRNs will be rooted in their focus on real-world clinical issues and their ability to generate information that will be of immediate value to practitioners and patients alike. For example, all three networks are collaborating to expand the evidence base on an emerging public health question: a suspected increased risk of a serious condition known as osteonecrosis of the jaw for individuals who have received therapy with a kind of drug known as bisphosphonates. Dental PBRNs have the potential to generate a body of high-quality clinical research data in a relatively short period of time. Most importantly, their research will substantially enhance the evidence base that clinicians use to inform treatment decisions, translate newer information into daily practice, and directly affect and improve care.

- For more information, see http://www.nidcr.nih.gov/Research/ResearchResults/InterviewsOHR/TIS062005
- For more information, see http://www.nidcr.nih.gov/Research/ResearchResults/NewsReleases/ArchivedNewsReleases/NRY2005/PR03312005.htm
- (E) (NIDCR)

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 2: *Minority Health and Health Disparities.*
- (E) (NIDCR)

Dialysis Access Consortium: Arteriovenous (AV) 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 AV fistulas and AV grafts. The AV Fistula Trial is evaluating the ability of clopidogrel to maintain access patency, while the AV Graft Trial is evaluating the ability of aspirin/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 2: *Chronic Diseases and Organ Systems*.

- (E) (NIDDK)

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 2: *Minority Health and Health Disparities*
- (E) (**OBSSR**, AHRQ, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINR, NIOSH)

Critical Issues in eHealth Research Conference: Toward Quality Patient Centered Care (September 2006): This second of two eHealth conferences served three purposes: (1) to highlight research methodologies that intersect across information technology, health communications, behavioral science, medical science, and patient care research, (2) to showcase existing and emerging technologies relevant to communications among patients and their health care teams, and (3) to discuss conceptual issues related to patient-centered eHealth research.

- Atienza AA, et al. *Am J Prev Med* 2007;32:S71-4, PMID: 17466821
- This example also appears in Chapter 3: *Technology Development*.
- (E) (**OBSSR**, NCI, ODP/ORD)

Research on Social Work Practice and Concepts in Health: Social workers focus on the creation of physical and mental health prevention and treatment interventions in order for individuals to become more productive members of society. As providers of front-line services in such areas as aging, teen pregnancy, child abuse, and substance abuse, particularly in underserved communities, they are in a unique position to provide valuable information on these complex social concerns. This initiative aims to incorporate unique social work concepts and perspectives into the NIH research portfolio and to build the scientific base for use by allied health professionals.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-292.html
- (E) (**OBSSR**, NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIMH, NINR, ODP/ORD, ORWH)

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. While 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: *Health Communication and Information Campaigns and Clearinghouses* and Chapter 2: *Minority Health and Health Disparities*
- (E) (*OBSSR*, AHRQ, NCI, NHLBI, NIA, NIBIB, NICHD, NIDCD, NIDCR, NIEHS, NIMH, NINR, NLM)

SBIR/STTR Management Redesign: The NIH Small Business Research programs, SBIR and STTR, serve to foster and encourage innovative research with the goal of transferring technologies and processes into commercial applications that will improve the health of the Nation. By March 2007, NIH established a working group (Trans-

NIH SBIR/STTR Think Tank Working Group) to develop an agency-wide strategy that aligns the SBIR/STTR program with crosscutting NIH program goals (e.g., the NIH Roadmap for Medical Research) and advances the agency's vision for translating scientific discoveries into commercial products and services by using SBIR/STTR strategically. Future efforts will include the development and implementation of a pilot SBIR/STTR initiative that would meet these objectives, foster effective public-private partnerships, and ensure a stronger, more integrated technology program.

- For more information, see http://grants.nih.gov/grants/funding/sbir.htm
- (O) (OD/OER)

Clinical and Translational Science Award (CTSA) Consortium: To remove barriers to clinical (including pediatric) research identified by research communities, NIH launched the Clinical and Translational Science Award (CTSA) program in September 2006. The program will more rapidly and efficiently facilitate the transfer of discoveries made in the laboratory into new strategies to prevent or treat disease. Through the CTSAs, academic health centers are forming a national consortium with interdisciplinary teams that cover the complete spectrum of biomedical research—from basic molecular biology to clinical medicine. The CTSA Consortium will design clinical research informatics tools, forge new partnerships with private and public health care organizations, expand outreach to minority and medically underserved communities, develop better designs for clinical trials, and train the next generations of clinical and translational researchers. Working together, the Consortium will adopt and disseminate best practices, policies, procedures, and other measures to advance collaborative clinical and translational research. The CTSA Consortium is the primary initiative for addressing the NIH Roadmap for Medical Research theme to Re-Engineer the Clinical Research Enterprise.

- For more information, see http://www.ctsaweb.org/
- (E) (Roadmap—all ICs participate)

Training Activities of the Clinical and Translational Science Award Program: Comparing new disease treatments and prevention strategies against those in current use requires dedicated clinical and translational research teams that include physicians, basic scientists, statisticians, and informatics experts, among others. Clinical research requires unique skills in addition to those needed to care for patients, so academic health centers must equip promising individuals with the special training they need to succeed in research careers. To address this need, NIH has expanded its clinical research training programs, first through the Roadmap T32 and K12 programs and, more recently, through Clinical and Translational Science Awards (CTSAs). Each program is based on placing the trainees in a mentored environment, where they learn the skills needed to cultivate multidisciplinary research team collaborations and design research projects to successfully compete for funding. The CTSA program will grow through 2012 to serve about 60 academic sites, providing research training and career development opportunities to a combined total of more than 1,200 trainees and new investigators covering multiple individual disciplines.

As mandated in Section 106 of the National Institutes of Health Reform Act (Pub. L. No. 109-482), NIH will conduct an evaluation and comparison of the outcomes and effectiveness of the CTSA training programs. This evaluation will be part of a much larger comprehensive evaluation of the CTSA program as a whole. Each individual CTSA is expected to include their training activities in their own evaluation. To coordinate and share information, including results of training activity evaluations, there is a CTSA Education/Career Development Steering Committee which provides a forum for the advancement of integrated and interdisciplinary education, training, and career development in the clinical and translational sciences and serves as a clearinghouse for clinical research training. Since the CTSA program was only recently initiated (September 2006), significant evidence of the long-term impact of the CTSA program is more likely to be measurable after 7 or more years. However, short-term process milestones and intermediate outcomes are expected in 1 to 7 years.

- For more information, see nihroadmap.nih.gov/clinicalresearch/overview-training.asp
- For more information, see http://www.ctsaweb.org/
- This example also appears in Chapter 3: *Research Training and Career Development*

- (E) (Roadmap—all ICs participate)

Reports of Clinical Trials Working Group (CTWG) and Translational Research Working Group (TRWG): Recognizing the importance of translational and clinical research, two major reports of comprehensive evaluations were recently released that 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 comprised experts from academia, the pharmaceutical industry, advocacy groups, NIH, and other governmental agencies) to review and evaluate the current portfolio of research being done in that area and 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 2: *Cancer*.
- (E/I) (NCI)

Clinical and Translational Science Award (CTSA) Program Evaluation: Given the ambitious goals of the CTSA program to transform the practice of clinical and translational science, NIH recognizes that rigorous attention must be given to evaluate the program's effectiveness in meeting those goals. NIH must ensure that program findings and outcomes are disseminated to stakeholders, including researchers, advocacy groups, Congress, and especially the patients who stand to benefit most from new prevention strategies and treatments reaching them faster. Therefore, NIH has launched a comprehensive evaluation of the CTSA program that will assess the impact of the CTSA Consortium on transforming translational and clinical research. The CTSA evaluation will proceed at both a national and an institutional level, allowing NIH to assess national, Consortium-wide goals while providing flexibility for the individual CTSAs to evaluate components unique to their specific CTSA.

- For more information, see http://www.ctsaweb.org/
- (E) (NCRR)

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 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
editation based in traditional Chinese medicine, experienced significant augmentation in levels of immunity to the
us that causes shingles following vaccination against the virus. Other investigators have demonstrated that
tients with chronic heart failure show improvements in quality of life, exercise ability, and biomarkers of cardiac
alth 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
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NCCAM)

Summary of Research Activities by Key Approach and Resource

Disease Registries, Databases, and Biomedical Information Systems

The Atlanta physician had never before treated a boy complaining of "numb chin." He sent the lad to the examining room to undress and quickly turned to his personal computer. He typed in the term "numb chin" and read from the screen a lengthy description of an article on just that subject. This information provided the vital clue the physician needed to diagnose a form of lymphoma. Similar scenes are reenacted thousands of times every day in physicians' offices, research laboratories, hospital nurses' stations, and medical schools–in short, wherever health professionals require information. The system this physician tapped into is MEDLINE, just one of the National Library of Medicine's growing numbers of online databases containing medical references, abstracts, and other essential health information for professionals as well as the general public.

Introduction

From bench to bedside and from database to desktop, information itself has become a primary driver of progress in the biomedical and health care enterprise. For example, the volumes of data resulting from sequencing the genomes of thousands of patients have become primary resources for identifying associations between specific genes and diseases. The data that flow from large-scale clinical studies, advanced diagnostic and imaging equipment, and electronic medical records is a key enabler of improvements in clinical practice and individual patient care. Up-to-date information from disease registries has become a critical resource for studying disease incidence and treatment patterns and forms the basis for public health interventions. The availability of this and other health information on the Internet enables consumers to play a more active role in managing their health and further increases demand for reliable and authoritative health information.

The development, deployment, and utilization of disease registries, databases, and other biomedical information systems are essential to managing large amounts of data for improved health. Such systems permit the efficient collection, storage, and accessing of biomedical information. Disease registries collect information about the occurrence of specific diseases, such as cancer and Parkinson's disease, the kinds of treatment that registered patients receive, and other information that might be relevant to researchers or public health officials. This information can help in identifying causal factors of disease, assessing the effectiveness of various interventions, and identifying questions of concern to researchers, clinical professionals, and policymakers. Biomedical databases serve as repositories for a wide range of information, from the results of scientific or clinical research studies, to genomic information, to standard reference materials (such as genome sequences or anatomical images), to published journal articles and citations to the medical literature. They are widely used by biomedical researchers, as well as a growing number of clinicians, public health officials, and consumers.

Increasingly, biomedical databases serve not only as repositories of information, but also as research tools in and of themselves. Discoveries can be made by examining the information they contain. Scientists can use molecular databases to study the molecular profiles of individual tumors and create small-molecule anticancer agents to target them. They can analyze large-scale databases linking genotype and phenotype information from thousands of individuals to identify the genes associated with particular observable traits (e.g., obesity) or diseases (e.g., diabetes, cancer). In these ways, biomedical information systems are changing the nature of research itself, and promise to change the nature of clinical care and public health.

The utility of biomedical information systems rests on many factors, including the quality of the data they contain,

accessibility to the full range of potential users, how easily they can be searched to find relevant and interesting results, and the availability of useful tools for analyzing the information they contain. New data must be added on a regular basis, while existing data are maintained or updated to reflect new findings. Improved search tools are needed to comb through the massive datasets and retrieve relevant results. Standard vocabularies that are used to organize information and ensure accurate retrieval must be updated to accommodate new concepts and relationships. New analytical tools are needed to explore increasingly complex questions, such as how the expression patterns of multiple genes are associated with a particular trait or response. Preserving, protecting, and ensuring the validity and security of information stored in biomedical databases remains of paramount importance.

Scope of NIH Activities in Disease Registries, Databases, and Biomedical Information Systems

Because of the growing importance of information and its management in biomedical science, clinical care, and public health, virtually every NIH IC is engaged in the development, deployment, and use of biomedical information systems that support their mission. Several trans-NIH Roadmap activities also feature the development of significant biomedical information resources, including the tools, infrastructure, and associated research needed to make databases and registries more valuable.

Most evident among NIH's biomedical information resources are major scientific databases such as GenBank (genomic sequence data), PubChem (small molecules data), and dbGaP (database of Genotype and Phenotype). These and many similar databases (NLM alone oversees 36) have become indispensable national and international resources for biomedical and health research and public health. DNA sequence data stored at NIH, for example, allowed rapid identification of the first known polio case in the United States since 1999 and the rapid initiation of treatment.

NIH also houses the leading source of authoritative biomedical literature for professional and lay audiences. NLM's exhaustive Medline/PubMed database, for example, indexes citations to some 5,000 peer-reviewed scientific journals on a regular basis. PubMed Central, its digital archive of full-text articles, provides online access to a growing number of scientific journal articles deposited by publishers and by NIH-funded researchers who are complying with the NIH Public Access Policy. These comprehensive resources are widely used by scientists, health care providers, and consumers who seek peer-reviewed information on biomedical and health topics of interest. As another example, peer-reviewed studies from the National Toxicology Program are used by State, local, and Federal health officials to assess the toxicologic potential of environmental compounds to cause adverse health effects such as cancer.

NIH also works with other Federal and private entities to integrate disease registries for national and local use. For example, for 34 years the Surveillance, Epidemiology, and End Results (SEER) program has collected and published cancer incidence and survival data from cancer registries covering approximately 26 percent of the American population. SEER information has been the foundation for innumerable studies, including recent research into links between hormone therapy and breast cancer. NIAMS supports a dozen registries associated with specific diseases, including lupus, muscular dystrophy, and rheumatoid arthritis.

NIH's work on biomedical information systems goes beyond the establishment of databases and registries. NIH is also the largest Federal funder of biomedical informatics research, which aims to advance the applications of computing to biomedicine—for both research and clinical care. Grant programs support research and training in medical informatics and medical librarianship. NIH also leads the government's efforts to develop standardized vocabularies and terminology to support interoperability among biomedical information systems and has developed numerous tools to facilitate data analysis. These efforts aim to create and sustain the biomedical information infrastructure needed for research, clinical care (including electronic health records), and public health.

Summary of NIH Activities

Expanding and Enhancing NIH Scientific Databases

Keeping pace with the expanding biomedical knowledge base is a continuing challenge for scientists; thus, NIH devotes considerable attention and resources to developing, expanding, and maintaining tools and resources for information management. NLM's Medline/PubMed database of the peer-reviewed bioscience literature, for example, added almost 1.3 million new citations to its archive in the 2-year period of FYs 2006-2007 and now contains indexed citations of more than 17 million articles, editorials, comments, and other materials. PubMed Central, NIH's electronic archive of full-text journal articles, passed the 1 million article mark in June 2007. NIH's online registry of clinical trials, Clinicaltrials.gov, added information on more than 23,000 clinical research studies in FY 2006-2007 and by the end of FY 2007 contained information on some 47,000 clinical trials conducted in more than 140 countries. Many other NIH databases have seen similar growth, placing greater demand on NIH's information infrastructure and on the resources needed to input, store, and index information. Ongoing efforts are needed to streamline such processes and boost their productivity.

Increased utilization goes hand in hand with the expanding content of NIH's databases. Medline alone logged nearly 900 million searches in FY 2006, almost twice the level of FY 2003, and Clinicaltrials.gov saw some 500 thousand unique visitors in June 2007, double the number 2 years earlier. Some of this increase is attributable to an expanding scope of users—not just biomedical researchers, but also clinicians, consumers, and other practitioners. NIH actively endeavors to make its information resources more accessible to varied types of users, as illustrated by its work on MedlinePlus, NLM's comprehensive health information source for consumers and health professionals, and WISER, the Wireless Information System for Emergency Responders. WISER makes information available to emergency responders from NIH's TOXNET databases. TOXNET, is a cluster of 14 large databases covering toxicology, hazardous chemicals, environmental health, and related topics. It has been used by toxicologists for decades, assisting them in locating toxicology data, literature references, and toxic release information on particular chemicals, as well as in identifying chemicals that cause specific health effects. To make these resources more useful to first responders at the scene of a disaster, NIH developed the WISER system, which enables wireless access to a selection of the most relevant data for emergency responders. WISER can be installed on personal digital assistants, providing emergency personnel with access to critical information for identifying and safely cleaning up spilled chemicals, understanding their health effects, treating exposed victims, and assessing environmental impact. A Web-based version of WISER, released in FY 2006, can be accessed from any Web-enabled device. WISER was used to access information on dangerous chemicals to which Hurricane Katrina victims may have been exposed.

Genomic Information Systems

NIH also has made great strides in developing information resources to support genetics research. NIH has long supported genetic information resources through widely used repositories such as GenBank, the NIH genetic sequence database. More recent efforts have aimed to support the analysis of data from genome-wide association studies, which explore the connection between specific genes (genotype information) and phenotype information, such as observable traits (e.g., blood pressure, weight) or a particular disease. NIH's dbGaP (database of Genotype and Phenotype) was launched in December 2006 to house data from a number of genome-wide association studies. By the end of FY 2007, dbGaP contained more than 12 large datasets, including genetic analyses from the landmark Framingham Heart Study, and studies of age-related eye diseases and Parkinson's disease. The wide availability of information linking genotype to phenotype should help researchers better understand gene-based diseases and speed development of effective therapies.

Several NIH ICs have established genetics repositories to accelerate research and multidisciplinary collaborations in specific disease areas. Programs such as the NIMH Genetics Repository, the NINDS Human Genetics Repository, the NCBI Influenza Virus Resource, the NIA Genetics of Alzheimer's Disease Data Storage Site, and the National Database for Autism Research give researchers access to vast storehouses of genetic and genomic data, DNA

samples, and clinical data, along with informatics tools designed to facilitate their analyses. For example, the Influenza Virus Resource database, comprising information obtained from the NIAID Influenza Genome Sequencing Project and GenBank, contains more than 40,000 influenza virus sequences, including the sequences of more than 2,500 whole influenza genomes. More than 11,000 sequences were added in FY 2006, along with new search and annotation tools. This resource enables scientists to compare influenza virus strains so that emergent variants can be more rapidly identified and vaccines developed accordingly. As the library of viral sequences grows it will be an increasingly important reference to help further understand how avian viruses spread to humans, and how influenza activity spreads throughout the world.

Disease Registries and Surveillance Systems

NIH-supported disease registries have paid many dividends over the years. Recently, for example, with the participation of patients from the Alopecia Areata Registry , NIH-supported scientists discovered four chromosomal locations that appear to be associated with susceptibility to this common autoimmune disease, which is characterized by patchy hair loss. Understanding the mechanisms of the genes found at these locations could lead to the development of an effective treatment for the disease, which is presently untreatable.

Registries also serve as an effective mechanism to gather data on the incidence, prevalence, and natural history of diseases. The NIEHS-supported California Parkinson's Disease Registry, for example, enables researchers to identify the possible environmental and genetic origins of this progressive neurological disorder suffered by an estimated 1.5 million Americans. Data in the registry can help to determine whether race, ethnicity, gender, age, environmental factors, or place of residence influence the likelihood of getting the disease, and can help track incidence and demographic trends.

Registries also are integral elements of more comprehensive NIH programs designed to monitor and analyze disease trends in the United States. For example, the Surveillance, Epidemiology, and End Results (SEER) program has a rich track record of identifying emerging trends, geographic variation, ethnic disparities, and other patterns that have provided new directions for epidemiologic research in cancer etiology and control. SEER data provided critical insight into the relationship between hormone therapy and breast cancer incident rates. Reported incidents of breast cancer in the SEER registry began to decline in mid-2002, shortly after a highly publicized series of reports from the NIH Women's Health Initiative (WHI) revealed an association between the risk of breast cancer and the use of hormone therapy. By analyzing SEER data on breast cancer incidence rates using several key factors such as the estrogen-receptor status of tumors, WHI researchers demonstrated that the incidence of tumors most likely to be affected by changes in hormone therapy reflected usage patterns, while trends for other tumors did not.

Surveillance and monitoring programs are also crucial sources of information and analysis for policymakers, legislators, public health officials, clinicians, and the public. SEER participates in Cancer Control P.L.A.N.E.T. (Plan, Link, Act, Network with Evidence-based Tools), a Web portal that provides links to comprehensive cancer control resources and data for public health professionals. NIDA supports several epidemiologic programs designed to gather ongoing data and monitor emerging drug abuse trends in adolescents and other populations, helping to guide national and global prevention efforts, drug control, and public health policy. Among the projects is the Monitoring the Future (MTF) Survey, which has been tracking trends in substance use, attitudes, and beliefs among adolescents and young adults in the United States since 1975. Data from the 2007 MTF Survey show good news and continuing areas of concern. For although teen drug use continues to decline—including cigarette smoking, now at the lowest rate in the survey's history—use of prescription-type drugs is still high, with more than 15 percent of 12th graders reporting nonmedical use within the past year.

Enhancing the Utility of Data Resources: Tools and Standards

Other efforts aim to enhance the utility of NIH databases. A key element of this work is to exploit the inherent relationships among information in disparate databases. NIH's PubChem database, for example, is an integrated hub within the Entrez suite of biomedical information resources. PubChem is the repository for data flowing from the high-throughput bioassay centers that were established with NIH funding under the Molecular Libraries Initiative of the NIH Roadmap. It provides information about the biological activity of small molecules, organized as

three linked databases along with a chemical structure similarity search tool. PubChem's chemical structure and bioassay records are interlinked with the biomedical literature in PubMed and with three-dimensional protein structure records. This integration provides many routes by which biomedical researchers may discover the candidate probes developed by the Molecular Libraries Initiative. A researcher examining a protein sequence record, for example, may see that a particular protein has been screened, view the active compounds, and examine structure-activity relationships using PubChem analysis tools. NLM's Discovery Initiative, launched in FY 2006-2007, aims to take database linking to the next level. The Discovery Initiative will improve the presentation of results from search queries conducted across a range of NIH databases so that users, who often do not go beyond retrieving the basic results of a search query, are more likely to be drawn to related information that could lead to serendipitous discoveries, even if that information resides in another NIH database.

Other efforts relate to the development of standardized nomenclatures and data protocols. Medical terminology can be difficult to remember and can vary from one laboratory or clinical facility to another. Often there are many names for a single concept (e.g., cancer of the colon, colonic neoplasm, colon cancer). Standard vocabularies and ontologies (models of the relationships between concepts) improve information search and retrieval by endowing systems with the ability to automatically perceive and retrieve information about related terms. As expansion of the scientific frontiers produces new concepts, terms, and relationships, standard vocabularies must be regularly revised so that articles and other data can be properly indexed and search engines can find relevant and related terms.

NLM continues to update its Unified Medical Language System (UMLS), which is heavily used in advanced biomedical research and data mining worldwide. NLM and many other institutions apply UMLS resources in a wide variety of applications including information retrieval, natural language processing, creation of patient and research data, and the development of enterprise-wide vocabulary services. NIH's ClinicalTrials.gov database now uses the UMLS to improve the system's ability to retrieve information about clinical trials related to a user's interests.

UMLS and related NIH programs also contribute to efforts to national efforts to expand the use of electronic health records to improve the quality and efficiency of health care. Standardized clinical terminology and coding systems facilitate the exchange of information among care providers, insurers, and patients, contributing to implementation of an interoperable health information technology infrastructure. NLM is the government's lead agency for maintaining and disseminating clinical terminology standards. In 2007, NIH helped to establish the International Health Terminology Standards Development Organization, which is globally distributing SNOMED CT (Systematized Nomenclature of Medicine?Clinical Terms), a comprehensive clinical terminology for electronic health records.

Informatics/Computational Biology Initiatives

NIH also has embarked on a number of large-scale initiatives to develop and deploy infrastructure and tools for storing, sharing, integrating, and analyzing the large volumes of data routinely generated by today's laboratories.

In the area of cancer research, for example, NIH has established the cancer Biomedical Informatics Grid (caBIG). caBIG is a collaborative information network for all of NCI's advanced technology and program initiatives, connecting scientists, practitioners, and patients and enabling the collection, analysis, and sharing of data and knowledge along the entire research pathway from bench to bedside. Specific biomedical research tools under development by caBIG include clinical trial management systems, tissue repositories and pathology tools, imaging tools, and a rich collection of integrative cancer research applications. Patients benefit from caBIG through systems and services such as BreastCancerTrials.org (BCT), which was launched in 2006 to match patients' medical case histories to ongoing clinical trials in the greater San Francisco and Sacramento areas. Created by patients for patients, BCT is an online version of a caBIG tool called caMatch, which aims to save patients time and energy, while also giving them greater options in seeking clinical trials that are relevant to their condition.

Other efforts aim to provide the informatics infrastructure to advance basic research and clinical studies across the

spectrum of biomedical sciences. NIH's Biomedical Informatics Research Network, for example, is a virtual community of shared informatics resources. It includes a data repository that makes research data freely available for sharing and exchange; data integration tools that allow searching across distributed databases; and tools for data analysis, management, and collaborative research. The National Electronics Clinical Trials and Research (NECTAR) network, a clinical research "network of networks," is a Roadmap initiative that will provide the informatics infrastructure for interconnected and inter-operable clinical research networks. NECTAR will allow clinical investigators to broaden the scope of their research while enhancing efficiency and reducing duplication of efforts by integrating clinical research networks that currently operate independently of each other. Another Roadmap initiative will create a national software engineering system through Bioinformatics and Computational Biology initiatives. Through a computer-based grid, biologists, chemists, physicists, computer scientists, and physicians anywhere in the country will be able to share and analyze data using a common set of software tools. The National Centers for Biomedical Computing are a central focus of this effort.

Biomedical Informatics Research and Training

Ensuring continued advances in biomedical informatics resources requires active support of fundamental research that seeds the further development of new tools, resources, and approaches. It also is critical to generating a continuous supply of skilled biomedical informatics researchers, information specialists (such as medical librarians), and life sciences researchers trained in bioinformatics. NIH continues to expand its efforts in bioinformatics research and training in response to the growing importance of informatics in the biomedical and life sciences (see section on Research Training).

Several ICs fund informatics research projects within their areas of specialization. However, NLM remains the primary Federal sponsor of biomedical informatics research, and its extramural grants program supports research on the characterization, management, and efficient use of data, information, and knowledge in health care and basic biomedical sciences. Grants funded in FY 2006-2007 explored informatics challenges related to clinical care, biomedical research, genomics, and public health. NLM's long-range plan, *Charting a Course for the 21st Century*, published in September 2006, identifies a number of emerging informatics challenges that will demand continued research and development.

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

Scientific Databases

MEDLINE/PubMed and PubMed Central (PMC): NIH continued to expand MEDLINE/PubMed as a tool for biomedical research, clinical medicine and consumer health. Almost 1.3 million citations were added to MEDLINE/PubMed in FY 2006-2007, a 10 percent increase from the previous two-year period. NIH made significant strides in enhancing PMC, its repository of full-text biomedical journal articles. PMC surpassed the 1 million-articles mark in June 2007, and, to support NIH policy on public access to NIH-funded research, the NIH Manuscript Submission system was developed, enabling NIH grantees to deposit manuscripts into PMC. To foster international cooperation on preservation and access to biomedical literature, NIH made PMC software available to archiving

organizations outside the United States and worked with the Wellcome Trust and other major United Kingdom research funders in the to establish a UKPMC service. Five other countries plan to establish PMC sites.

- For more information, see http://www.pubmed.gov
- For more information, see http://www.nihms.nih.gov/
- For more information, see http://www.pubmedcentral.nih.gov/about/pmci.html
- For more information, see http://ukpmc.ac.uk/
- (I) (NLM)

MedlinePlus/MedlinePlus en Español: NIH employed new methods to increase awareness of its MedlinePlus databases. Weekly podcasts by NLM's Director were initiated to provide timely reports on health news; *NIH MedlinePlus The Magazine* was rolled out at a press event on Capitol Hill attended by members of Congress and guest celebrity Mary Tyler Moore, featured on the cover. The magazine is distributed free of charge to 40,000 physician offices and has covered stories on cancer, diabetes, and heart attack. NIH expanded the content and features of the English and Spanish MedlinePlus Web sites and the associated GoLocal sites that provide information on local health resources for approximately one-third of the U.S. population. MedlinePlus was one of two U.S. winners of the 2005 Award at the World Summit on the Information Society.

- For more information, see http://www.medlineplus.gov
- This example also appears in Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (I) (NLM)

TOXicology Data NETwork (TOXNET): TOXNET is a cluster of more than 10 databases covering toxicology, hazardous chemicals, environmental health, and related topics. It is a primary reference for toxicologists, poison control centers, public health administrators, physicians, and other environmental health professionals. In 2006, the Hazardous Substances Data Bank, which contains comprehensive information on more than 5,000 substances, was expanded to include a general record for ionizing radiation and a series of specific radionuclide records. In 2007, LactMed, a peer-reviewed and fully referenced database of drugs to which breast-feeding mothers may be exposed, was added to TOXNET.

- Wexler P. *Toxicology* 2004;198:161-8, PMID: 15138039
- Tomasulo P. *Med Ref Serv Q* 2007 Spring;26:51-8, PMID: 17210549
- For more information, see http://toxnet.nlm.nih.gov
- (I) (NLM)

National NeuroAids Tissue Consortium (NNTC): The NNTC is a repository of brain tissue and fluids from highly characterized HIV+ individuals. Established as a resource for the research community, the NNTC includes information from over 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*
- (E/I) (**NIMH**, NINDS)

ClinicalTrials.gov: Established in 2000 in response to congressional mandate (Pub. L. No. 105-115), ClinicalTrials.gov has grown to become the largest clinical trial registry in the world with information on clinical research studies for hundreds of diseases and conditions conducted in 148 countries. At the end of September 2007, it contained more than 47,000 registered trials—more than double the number of entries 2 years earlier. Legislation enacted in September 2007, the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85), expanded the scope of trials to be registered with ClinicalTrials.gov and the registration information to be provided. It also mandates the inclusion of specified results information beginning in September 2008.

- Drazen JM, et al. *N Engl J Med* 2007;356:184-5, PMID: 17215537
- Zarin DA, et al. *N Engl J Med* 2005;353:2779-87, PMID: 16382064
- For more information, see http://clinicaltrials.gov
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (I) (NLM)

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 over 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 2: *Infectious Diseases and Biodefense*, Chapter 3: *Molecular Biology and Basic Sciences*, and Chapter 3: *Genomics*
- (1) (NLM, NIAID)

PubChem: PubChem provides information on the biological activities of small molecules. It is a component of NIH's Molecular Libraries Roadmap Initiative. By the end of 2007, PubChem contained information on more than 38 million substances, 18 million compounds, and 710 bioassays.

- For more information, see http://pubchem.ncbi.nlm.nih.gov/
- (E) (Roadmap—all ICs participate)

Databases for Cervical Cancer Research: NIH has developed data analysis and image recognition tools for studying biomedical images of human papillomavirus (HPV) infection and cervical neoplasia. Image data include 100,000 cervicographs (high-definition cervical photograph), 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 2: *Cancer*.
- (I) (**NLM**, NCI)

Genomic Information Systems

Database of Genotype and Phenotype (dbGaP): Research on the connection between genetics and human health and disease has grown exponentially since completion of the Human Genome Project in 2003, generating high volumes of data. Building on its established research resources in genetics, genomics and other scientific data, NIH established dbGaP to house this growing body of information, particularly the results of GWAS, which examine genetic data of subjects with and without a disease or specific trait to identify potentially causative genes. By the end of 2007, dbGaP included results from more than a dozen GWAS, including genetic analyses added to the landmark Framingham Heart Study and trials conducted under the Genetic Association Information Network. dbGaP is to become the central repository for many NIH-funded GWAS in order to provide for rapid and widespread distribution of such data to researchers and accelerate the advance of personalized medicine.

- For more information, see http://view.ncbi.nlm.nih.gov/dbgap
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Genomics*.
- (I) (NLM)

Genome-Wide Association Studies (GWAS) and Database of Genotype and Phenotype (dbGaP): In December 2006, NIH released the initial dbGaP dataset using genome-wide association 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. In order 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 controlling for other factors, certain forms of the genes increased risk of AMD progression 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E) (**NEI**, NIA, NLM)

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-serving 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (NIMH)

NINDS Human Genetics Repository: In 2003, NINDS established this 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 stroke (4,363), epilepsy (1,065), Parkinson's disease (3,585), motor neuron diseases such as ALS (2,445), and 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E/I) (NINDS)

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 2: Chronic Diseases and Organ Systems and Chapter 3: Genomics.
- (E) (NHLBI)

Alzheimer's Disease (AD) Genetics Initiative and Data Storage: Only one of the four validated AD 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 (LOAD) in some studies. The goal of the AD Genetics Initiative is to develop the resources necessary for identifying the LOAD 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 AD through an unprecedented alliance of AD Centers, researchers, and outreach with the Alzheimer's Association. To facilitate access by qualified investigators, all genetic data derived from NIH-funded studies on LOAD 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 AD, 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 2: Neuroscience and Disorders of the Nervous System.
- (E/I) (NIA)

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 2006;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
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2006/lupus_susceptibility_gene.asp
- This example also appears in Chapter 2: *Autoimmune Diseases*.
- (E) (NIAMS, NCRR, NHLBI, NIAID, NIMH)

Disease Registries and Surveillance Systems

Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS): In a joint effort, NHLBI, the Center for Medicare & Medicaid Services, and the U.S. Food and Drug Administration 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 2: Chronic Diseases and Organ Systems and Chapter 3: Technology Development.
- (E) (NHLBI)

Resuscitation Outcomes Consortium: Recognizing the critical importance of early intervention for victims of cardiopulmonary arrest and traumatic injury, in FY 2004 NIH and its U.S. and Canadian partners initiated the Resuscitation Outcomes Consortium, a large-scale network to conduct clinical trials of promising approaches to improving outcomes. During FY 2006-2007, two Consortium clinical trials began enrolling patients—one to compare the efficacy of three fluids for initial resuscitation of hypotensive or brain-injured patients and the other to test two strategies for increasing blood flow during cardiopulmonary resuscitation. The Consortium also

established a pre-hospital Cardiac Arrest and Trauma Registry across the United States and Canada. In addition, emergency medicine fellowship training programs established at several study sites are enhancing training in resuscitation medicine.

- For more information, see https://roc.uwctc.org/
- This example also appears in Chapter 3: Clinical and Translational Research.
- (E) (NHLBI, NINDS)

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 towards 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 multi-city epidemiological network on drug abuse.

- For more information, see http://www.monitoringthefuture.org/
- For more information, see http://www.drugabuse.gov/about/organization/CEWG/CEWGHome.html
- This example also appears in Chapter 3: Epidemiological and Longitudinal Studies and Chapter 2: Minority Health and Health Disparities.
- (E) (NIDA)

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, provide 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 2: Neuroscience and Disorders of the Nervous System.
- (E) (NIEHS)

Surveillance, Epidemiology, and End Results (SEER) Program and Software Analysis Tools: The program is an authoritative source of information on cancer incidence and survival in U.S. publications, such as the Annual Report to the Nation on the Status of Cancer, or interpretation of recent declines in breast cancer incidence to inform the public, researchers, Federal and private agencies, and Congress on national cancer rates and trends. SEER is the only comprehensive source of population-based information in the United States 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, to analyze and disseminate data, and to 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 2: Cancer.
- (E) (NCI)

Gene Expression Changes in Facioscapulohumeral Muscular Dystrophy (FSHD): Results from a genome-wide scan of skeletal muscle biopsies suggest a link between eye blood vessel defects and muscle defects that characterize FSHD. Patient subjects were recruited from the National Registry for Myotonic Dystrophy and FSHD Patients and 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 2: Neuroscience and Disorders of the Nervous System and Chapter 3: Genomics.
- (E) (NIAMS, NCRR, NINDS)

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 2: *Autoimmune Diseases.*
- (E) (NIAMS, NIMH)

Enhancing the Utility of Data Resources: Tools and Standards

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 provide not only access to tools and resources, but also ongoing opportunities for public comment in order 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/
- For more information, see http://neuroscienceblueprint.nih.gov/
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*

- (E) (**NIBI**B, NCCAM, NCRR, NEI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

Health IT Standards: NIH's UMLS Metathesaurus is a distribution mechanism for standard code sets and vocabularies used in health data systems. NIH supports, develops, or licenses key health terminologies to enable their free use in U.S. electronic health record systems. In 2007, NIH helped to establish the International Health Terminology Standards Development Organization to promote more cost-effective maintenance and international adoption of the SNOMED CT clinical terminology. NIH supports ongoing development and distribution of the LOINC nomenclature for laboratory tests and patient observations and produces RxNorm, a standard clinical drug vocabulary. Another NIH resource, the Daily Med, is an official distribution mechanism for FDA-approved packaging information (drug label inserts) that links to other sources of drug information, including NIH's MedlinePlus, ClinicalTrials.gov, and PubMed. More than 60,000 people subscribe to its RSS data feeds.

- For more information, see http://www.nlm.nih.gov/healthit.html
- (I) (NLM)

UMLS Knowledge Sources: NIH's Unified Medical Language System® (UMLS) aims to facilitate the development of computer systems that behave as if they understand the meaning of biomedical and health terms. The UMLS tools underpin many production information retrieval systems at NLM and elsewhere and are heavily used in advanced research in biomedical natural language processing and data-mining across the country and around the world. The most recent UMLS Metathesaurus contains more than 1.3 million biomedical concepts and 6.4 million concept names from more than 100 source vocabularies.

- For more information, see http://www.nlm.nih.gov/research/umls/
- (I) (NLM)

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 2: *Infectious Diseases and Biodefense.*
- (I) (NLM)

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 2: *Chronic Diseases and Organ Systems.*
- (E) (Roadmap—all ICs participate)

The Cancer Control P.L.A.N.E.T: This 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 the resources that help them determine cancer risk and the 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 2: *Cancer.*
- (E) (NCI)

Informatics/Computational Biology Initiatives

Biomedical Informatics Research Network (BIRN): Modern biomedical research generates vast amounts of diverse and complex data. Increasingly, these data are acquired in digital form, allowing sophisticated and powerful computational and informatics tools to help scientists organize, store, query, mine, analyze, view, and, in general, make better use and sense of their data. Moreover, the digital form of these data and tools makes it possible for them to be easily and widely shared across the research community at large. NIH has supported development of the BIRN infrastructure to share data and tools by federating new software tools or using the infrastructure to federate significant datasets. BIRN fosters large-scale collaborations by utilizing the capabilities of the emerging national cyberinfrastructure. The project includes a Coordinating Center at the University of California, San Diego, which serves the critical task of developing, deploying, and maintaining key infrastructure components, including high-bandwidth connectivity, grid-based security, file management and computational services, techniques to federate databases, and shared visualization and analysis environments.

- For more information, see www.nbirn.net
- This example also appears in Chapter 3: *Technology Development.*
- (E) (NCRR)

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: *Life Stages, Human Development, and Rehabilitation* and Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E/I) (**NIMH**, CIT, NICHD, NIDCD, NIEHS, NINDS)

National Centers for Biomedical Computing (NCBCs): The NIH Roadmap Bioinformatics and Computational Biology initiative provides a networked national effort to build computational tools and infrastructure for biomedical computing. The centers are devoted to all facets of biomedical computing, from basic research in computational science to providing the tools and resources that biomedical, clinical, and behavioral researchers need to do their work. The seven centers currently supported by the NIH Roadmap have made substantial progress in software development, data resources, and scientific ontologies. These advances are currently being used by the research community for studying a broad range of biological problems including cerebral palsy, autism, diabetes, asthma, Alzheimer's disease, Huntington's disease, schizophrenia, bipolar disorder, HIV/AIDS, and prostate cancer. The long-term goal of the initiative is to create a national software engineering system that will enable biomedical and clinical researchers to share and analyze data using a common set of software tools.

- For more information, see http://nihroadmap.nih.gov/bioinformatics/
- This example also appears in Chapter 3: *Technology Development.*
- (E) (Roadmap—all ICs participate)

Biomedical Informatics Research and Training

Discovery Initiative: The Discovery Initiative aims to maximize the utility of NIH biomedical data resources by better exploiting their inter-linkages. For example, a PubChem record on a chemical structure might link to records for similar proteins, related protein structures, and relevant journal articles. Such linkages provide users with tremendous opportunities for exploration and scientific discovery but are currently underutilized. The Discovery

Initiative aims to improve the retrieval and presentation of results so that users are more readily drawn to related data that could lead to serendipitous discoveries.

- (I) (NLM)

Informatics Training for Global Health: Information technology is required in almost all research programs, both to access the vast information resources available internationally and to apply to research design and analysis. This program is intended to increase the capacity of developing country scientists and medical professionals to design, access, and use modern information technology in support of health sciences research. Specifically, this program supports innovative training programs for developing country biomedical and behavioral scientists and engineers, clinicians, librarians, and other health professionals to increase their capacity to access, manage, analyze, interpret, manipulate, model, display, and share biomedical information electronically. Among other skills, this will increase their ability to conduct multisite clinical trials and international disease surveillance and prevention programs.

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

Informatics Research Training Programs: To address the national need for computational scientists competent in biology and medicine, NLM reviewed its University Informatics Research Training Programs and issued a new call for applications. Curricula were updated to reflect current computing needs in clinical translational research and public health. Eighteen 5-year grants, totaling more than $75 million, for research training in biomedical informatics, were awarded in 2006. Approximately 270 trainees are currently enrolled in these programs.

- For more information, see http://www.nlm.nih.gov/ep/AwardsTrainInstitute.html
- This example also appears in Chapter 3: *Research Training and Career Development.*
- (E) (NLM)

Summary of Research Activities by Key Approach and Resource

Technology Development

In July of 2002, a U.S. team of surgeons performed surgery on a patient by remote control 4,000 miles away in France. The surgeons were in New York, where they monitored the patient on the screen as they used tools connected to hi-tech sensors. The sensors turned the movement of the surgeon's hands into signals that sped across the Atlantic through fiber-optic lines to guide robots that operated on a 68-year-old woman in Strasbourg. The patient had no complications and was discharged 2 days later. The 54-minute procedure, dubbed "Operation Lindbergh" in honor of Charles Lindbergh's solo flight across the Atlantic, was the first of its kind. This technological milestone raises the possibility of remote robot surgery on wounded soldiers on battlefields, astronauts in space, and individuals in remote rural settings. Also, patients needing particularly difficult surgeries may have worldwide access to top surgeons without the need to travel.

Introduction

NIH support of technology development has triggered a revolution in the understanding of health and disease. A notable example is the Human Genome Project (jointly funded by NIH and the Department of Energy), which culminated in the sequencing of the human genome. Technology development, ranging from rapid DNA sequencing machines to complex computational tools to assemble the sequences, was critical to the successful sequencing of the human genome, as well as the genomes of numerous other organisms. This led to the development of a comprehensive map of human genetic variation and improved understanding of fundamental biological processes. This new knowledge continues to fuel the development of new clinical treatments, improving patient outcomes and quality of life.

During the past several decades, scientists have developed new technologies to create innovative animal models that closely mimic complex human disease. For example, through genetic engineering, a mouse model was created that mimics Alzheimer's disease. NIH-funded researchers are now using this model to study disease progression in the degenerating brain. This research is further enabled by the technological development of new imaging tools used to track the degeneration. This work provides an important step in the pathway to the discovery of new medications to treat Alzheimer's disease and perhaps change its course. Biotechnology and nanotechnology are examples of technology development. Biotechnology combines disciplines like genetics, molecular biology, biochemistry, embryology, and cell biology, which are in turn linked to practical disciplines like information technology, robotics, and bioengineering to enable the development of new or enhanced tools and devices to further basic scientific research as well as lead to improvements in human health. Nanotechnology refers broadly to a field whose unifying theme is the control of matter on the molecular level in scales smaller than one thousandth of a millimeter and the fabrication of devices within that size range. It is a highly multidisciplinary field, drawing from fields such as applied physics, materials science, supramolecular chemistry, and mechanical and electrical engineering.

Other examples of major breakthroughs spurred by NIH-supported technology development include:

- Progress in physical therapy for stroke survivors using wearable upper extremity robotic devices to mimic normal arm movements
- A new method of communication via a brain/computer interface for individuals with amyotrophic lateral

sclerosis and other neuromuscular disorders
- Improved epilepsy surgery outcomes using an integrated imaging system with precision-guided surgery to remove seizure-causing regions in the brain
- New diagnostic and imaging methods for the early detection of cancer and other diseases
- Innovative high-throughput methods for detecting and characterizing disease-causing alterations in genes and proteins
- Sensor technologies combining multiple analytical functions into self-contained, portable tabletop devices that can be used by non-specialists to rapidly detect and diagnose disease
- Cochlear implants to restore hearing to hearing-impaired individuals
- Left ventricular assist devices to aid the failing heart
- New treatments for abnormal heart rhythms such as atrial fibrillation

The interactions among technology development, basic research, and clinical application drive the engines of biomedical research, enabling scientists and clinicians to use sophisticated tools to unravel fundamental biological questions that underlie health and disease, as well as to develop new therapies considered inconceivable just a few years ago. For example, technological developments in electrodes, computers, and materials were critical in developing the scientific understanding of the nature of some abnormal heart rhythms. Those same basic technological developments are now critical for treatment of abnormal heart rhythms using advanced imaging and ablation techniques.

Interdisciplinary or team research offers one of the best opportunities to develop new technologies and refine current ones. A team approach may identify problems and develop innovative solutions more quickly than a researcher working alone. NIH fosters and cultivates cooperative research so that fundamental discoveries and tools can be developed, even when their specific applications might not be obvious. For example, the laser was originally developed in the context of communication research. In medicine, the technology has been adapted to invent microscopes that are critical to many research areas as well as a variety of surgical tools including systems for laser eye surgery. Continued success in the future will require strong linkages among engineering, clinical medicine, physical science, computational science, and the biological sciences.

Scope of NIH Activity in Technology Development

To truly revolutionize medicine and improve human health, scientists need a more detailed understanding of the vast networks of molecules that make up cells and tissues, their interactions, and their regulation. Researchers also must have a more precise knowledge of the combination of molecular events leading to a given disease. In 2002, NIH recognized that a gap existed in the support of crosscutting technology development. In response to that need, the NIH Roadmap theme, New Pathways to Discovery, was initiated to advance understanding of biological systems and build a better “toolbox” for medical research in the 21st century. To capitalize on the completion of the human genome sequence and recent discoveries in molecular and cell biology, the research community needs wide access to technologies, databases, and other scientific resources that are more sensitive, robust, and easily adaptable to researchers’ individual needs. The NIH Roadmap is supporting the development of these resources through five components of the New Pathways to Discovery theme, including Building Blocks, Biological Pathways, and Networks; Molecular Libraries and Molecular Imaging; Structural Biology; Bioinformatics and Computational Biology; and Nanomedicine. The Roadmap was created to fulfill the need to apply crosscutting technology to numerous biomedical research and health challenges.

Technology development for a specific disease or organ system is supported by the relevant disease-specific NIH Institute. For example, NHLBI supports technology development to treat abnormal heart rhythms and stroke while NCI supports the development of technology to more effectively diagnose and treat cancer. In addition to the disease-specific Institutes, NIBIB and NCRR support broad areas of technology development and infrastructure. For example, NIBIB's mission is to improve health by leading the development and acceleration of the translation of biomedical technologies. NIBIB supports interdisciplinary research aimed at developing fundamental or crosscutting technologies that can be translated into several biomedical applications. This work often is done in collaboration with a disease-specific Institute as the work moves closer to clinical application. Similarly, NCRR

provides laboratory scientists and clinical researchers with the research infrastructure and tools to develop technology to understand, detect, treat, and prevent a wide range of diseases.

Recognizing the potential benefits to human health to be realized from applying and advancing the field of bioengineering, the Bioengineering Consortium (BECON) was established at NIH in 1997. BECON is composed of senior-level representatives from each of the NIH Institutes as well as other Federal agencies. BECON's mission is to foster new basic understanding, collaboration, and transdisciplinary initiatives among the biological, medical, physical, engineering, and computational sciences—all important and necessary components in technology development.

NIH supports technology development through several complementary mechanisms, including:

- High-risk, innovative projects with very little preliminary indication of the likelihood of success but a potentially significant impact (e.g., R21 funding mechanism). These projects may have small budgets and short timeframes, aimed at proof of principle.
- Research project grants with a sound basis in preliminary data, directed at development of a particular technology; some projects may take only a few years while others continue for a decade or more.
- Bioengineering research partnerships, which bring together multiple disciplines such as engineering, cell biology, physics, and neurology to develop solutions to specific biomedical questions or diseases.
- Specialized centers that represent a critical mass of expertise and technology, in which multidisciplinary development of complex, often unique technologies is pursued, typically in the context of challenging research problems that cannot be approached with existing tools. The Biomedical Technology Research Resources program creates these unique technologies, applies them to the most challenging problems in biology and medicine, and disseminates these capabilities into the broader research community. This program serves as an engine for translation of advances in the physical sciences into tools for biomedical and clinical research.
- Small business grants foster highly innovative projects to bring technological advances into the marketplace for the broadest possible availability and impact. These programs allow NIH to leverage the unique resources and perspectives available in the private sector to complement the work done at universities.

Summary of NIH Activities

Toward a New Era in Medicine

By 2030, just over 970 million people will be age 65 years or older worldwide. Medical advances will increase life expectancy and make acute diseases less frequent. However, chronic diseases and disabilities will have a major impact on health care in terms of both costs and patient management[10]. Health care in the future must be prepared to manage the challenges of an older population as well as continue to improve quality of life for younger individuals. Developments in technology will be central to the scientific advances that will lead to predictive, personalized, and preemptive medicine to equip our health care system to meet these challenges.

One example from past advances illustrates the potential of new technologies. A major breakthrough in the last 30 years, the cochlear implant, is an electronic device that gives individuals who are profoundly deaf or severely hard of hearing an opportunity to experience sounds. Although the device does not restore normal hearing, it does enable these individuals to understand and discern not only sounds in the environment but human speech as well. In the United States about 22,000 adults and nearly 15,000 children have received the implant. NIH has supported the initial development and continuing improvements of this technology over the past 30 years. According to scientists, profoundly deaf children who receive an implant at an early age develop language skills at a comparable

[10] For more information, see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5206a2.htm

rate to children with normal hearing. This device is allowing researchers to undertake large studies to determine how treatments such as the cochlear implant lead to better speech and language acquisition, academic performance, and economic outcomes for children with the implant. Results from these studies could lead to new recommendations for early intervention among infants who are profoundly deaf[11].

The research pipeline is replete with similar examples of NIH's commitment to technology development, its foresight in identifying emerging needs and emerging areas of investigation, and its ability to foster the development of technology that links basic research with clinical applications. Advances in research will continue to alter conventional medicine and lifestyle and NIH-supported technology development initiatives are central to improved understanding of scientific processes as well as improvements in health care. The following is an overview of technology development activities at NIH.

Gene Sequencing and Beyond

Mapping the human genome has created the opportunity to predict which individuals or groups may develop a disease or condition. To enter an era where personalized medicine is more readily available, in which specific genetic differences conferring susceptibility to disease can be easily determined and tailored therapies provided, researchers will need innovative sequencing technologies that are more efficient and cost-effective than current approaches. Relatively inexpensive sequencing devices would enable clinicians to tailor prevention, diagnosis, and treatment to each individual's unique genetic profile. To this end, NIH is awarding "$1,000 Genome Grants" to develop breakthrough technologies that will enable an entire human-sized genome to be sequenced for $1,000 or less. Currently, only analyses of ~ 500,000 Single Nucleotide Polymorphisms (SNPs) are being performed commercially at this cost; an individual's complete genome sequence (~ 3 billion base pairs) would offer vastly more information. Researchers will investigate use of nanotechnology, spectroscopy, and lab-on-chip approaches to find low-cost approaches to sequencing DNA. Lab-on-chip devices integrate multiple laboratory functions on a single microelectromechanical device of only millimeters to a few square centimeters in size.

Probing Proteins

Information from the Human Genome Project is now helping scientists as they begin to study proteins, the tiny powerhouses within cells responsible for cell function. Each protein is encoded with a specific sequence based on information found in genes but few tools have been available to examine protein structures and functions. A better understanding of protein activities could provide important information on why a disease develops. It also could lead to targeted drug therapies. As a result of the NIH-sponsored Protein Structure Initiative (PSI), investigators now have a more potent set of tools to examine the protein in three dimensions. Many of the technologies conceptualized during PSI's first phase have been commercialized and are being used in laboratories. Some of the developments include:

- Miniaturization of samples needed to grow, purify, and crystallize proteins
- Robotic systems to handle samples and image crystals
- Enhanced software to analyze structural data and create higher resolution images
- More accurate screening processes to detect crystals suitable for imaging
- Improved systems for making proteins from machines instead of cells

These advances have reduced the cost, time, and space needed to carry out structural studies and have improved the generation and analysis of quality data[12]. By visualizing protein structures, researchers gain a better understanding of many of the biochemical processes related to health and disease. This information also can be used to design drugs that target specific parts of a bacteria, virus, or tumor. Recently, PSI-funded scientists

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[11] Nicholas JG, Geers AE. *Ear Hear* 2006;27:286-98, PMID: 16672797

[12] For more information, see http://www.nigms.nih.gov/News/Results/110606a.htm

discovered a protein thought to be responsible for a lethal bacterial infection that affects the lungs of cystic fibrosis patients. Following this discovery, another set of researchers designed an experiment that provided important information on how the bacteria work. This collaborative effort could result in the development of a new drug to treat the infection.

Insights From Animal Models

Another key tool in discovering how a gene or protein malfunctions and causes disease is the use of animal models of disease. Over the last 25 years researchers have bred countless animals with deliberately altered genes that serve as models for studying normal and disease states. These "transgenic" animal models are assisting in fundamental research for a broad range of diseases and conditions. For example, NIH-supported scientists have developed various animal models of human cancer including breast, colon, lung, and others. These models are being used in cancer drug development to answer fundamental questions of drug pharmacology and toxicity. This knowledge is essential to the design of Phase I clinical trials in which the safety, dose level, and response to a new drug are studied in humans. NIH-supported researchers are also using mouse models whose brains contain genetically altered neurons to study how Alzheimer's and Parkinson's diseases mediate brain activity. In this research investigators activate or inhibit neurons using specific light frequencies. The work could be extended to clinical application by targeting neurons or cells involved in the disease process. In the case of Parkinson's disease, electrode-based deep-brain stimulation provides symptomatic relief but also can have side effects. Optical therapeutics that target diseased neurons could offer more precise therapy with fewer side effects[13].

Imaging Biological Systems

Better tools and techniques to understand activities within cells, tissues, and organ systems enable researchers to probe deeper to gain an understanding of the biological systems and networks that control both normal function and diseased states. For example, an NIH-funded team created a new optical microscope that permits scientists to see proteins that make up individual structures in a cell. The technique, known as photoactivated localization microscopy (PALM), may enable researchers to examine, for example, the proteins that control the organization and growth of HIV, the virus that causes AIDS. This information could be used to identify targets for drug development to halt viral replication.

Noninvasive molecular imaging using positron emission tomography (PET) and magnetic resonance imaging (MRI) is a fast developing area of research. By itself PET reveals information about such processes as metabolism or gene expression and is a key tool in basic cancer research as well as in providing clinical information for diagnosis and treatment of cancer patients. MRI provides information on anatomical structures. Two NIH-supported groups are developing imaging systems that combine PET and MRI. This research could lead to further understanding of how drugs disperse after administration; cardiac, central nervous system, and tumor cell metabolism; and mapping of neuroreceptors in small-animal brains. None of this is possible using current technology. A second group recently announced the first images of the human brain with a combined PET/MRI system. PET/MRI studies could allow clinicians to more definitively determine cognitive impairment and atrophy[14].

Image-Guided Interventions

To detect disease in its earliest stages, and thereby preempt it before symptoms appear, clinicians will need to examine smaller, more localized areas of the body. Image-guided interventions (IGI)—treatments or procedures that precisely target areas within the body with the aid of imaging techniques such as MRI or computed tomography (CT)—enable clinicians to look beneath the surface anatomy to visualize underlying pathology. As a result, images can be used to navigate the anatomy for biopsy and treatment of disease. In addition to diagnosing at-risk individuals, IGI may offer a safer, less invasive approach to many surgical procedures. Compared with

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[13] Zhang F et al. *Nature* 2007;446:633-9, PMID: 17410168

[14] Judenhofer MS et al. *Radiology* 2007;244:807-14, PMID: 17709830

traditional open surgery, minimally invasive procedures result in less tissue trauma, less scarring, and faster postoperative recovery time, which translates into shorter hospital stays and a more rapid return to family and work.

As an emerging clinical tool, IGI shows great promise but is hindered by a number of factors[15]. An NIH-sponsored workshop noted that collaboration was one of the biggest hurdles facing the field. Interdisciplinary research and collaboration in the fields of biology, medicine, computer science, physics, and engineering will help create fast, reliable, and cost-effective IGIs.

Technological advancements require:

- More refined robotics technology for surgery and biopsies
- Expanded data integration
- Improvements in real-time modeling and three-dimensional visualization techniques
- Better approaches to image acquisition

Diagnostics and Point-of-Care Technology

Ideally, patients would have access to high-quality and consistent health care and treatment regardless of where they live. Realizing this vision necessitates the development of portable, reliable, and inexpensive equipment. To achieve this will also require the leveraging of technologies developed in other fields such as telecommunications. Advances in fiber-optic and wireless communications devices allow physicians to engage in telemedicine, or the transmission via the Internet of medical information, to communicate with other physicians or pathologists thousands of miles away. In Tucson, Arizona, for example, a breast health center provides same-day mammogram, biopsy, and diagnosis of breast cancer to women in rural locations using a pathology tool developed by NIH-funded engineers. By combining rapid tissue processing with telepathology and teleoncology, cancer diagnosis times have dropped to a matter of hours rather than a 1- to 2-week wait.

Point-of-care technologies for use in pathology laboratories, emergency rooms, doctors' offices, and homes will be a key component of the evolving health care system. Current devices range from handheld glucose monitoring systems used by diabetics to monitor their blood sugar levels, to laptop-sized ultrasound scanners. Among the technologies on the horizon is a laboratory analyzer developed with NIH support that can identify specific bacteria responsible for urinary tract infections from a single drop of urine and do so in a matter of minutes rather than the 48 hours normally required in standard cultures.

Recent NIH-supported efforts in the design and microfabrication of electronic, optical, mechanical, and fluidic components for sensors and imaging devices have led to major advances in laboratory sample analysis. Several efforts target portable diagnostic platforms. One group has created a user-friendly miniaturized system that precisely measures levels of various antibodies, antigens, and nucleic acids found in saliva. The prototype is a low-cost disposable device that processes small amounts of saliva, amplifies its DNA, and detects the levels of DNA sequences of interest. Another group has developed a product to improve oral cancer detection. Created for dental office use, the handheld device emits a cone of light into the mouth that causes molecules within the cells to fluoresce. Normal oral tissue emits a pale green fluorescence while early oral tumor cells appear dark green or black.

Understanding the role that environment plays in the disease process requires accurate quantitative assessment. One novel NIH program aims to support development of technologies that make precise quantitative measurements of personal exposure to environmental chemical/biological agents, diet, physical activity, and psychosocial stress. Relatively inexpensive, lightweight, portable monitors and sensors such as wristbands, watches, or phones can be used to relay data from an individual to a central collective data bank.

[15] From Final Report of the Image-Guided Interventions 2004 Workshop, May 13-14, 2004, Bethesda, Maryland..

NIH, along with the National Science Foundation, sponsored a workshop in 2006 to assess technological developments needed for advances in point-of-care testing and to identify clinical problems that could benefit from a point-of-care approach. As a result, NIH is supporting a program designed to create a national network of expertise to develop technologies that will address unmet clinical needs in global health, early detection of neurological emergencies (strokes), and detection of pathogens in emergency and disaster situations.

While some technologies have experienced widespread acceptance, several barriers must be overcome to make point-of-care diagnostics the norm. These include:

- Combining individual components into fully integrated systems that can handle all aspects of analysis
- Capturing data from these devices and transmitting it to clinical information systems
- Facilitating assessment of clinical opportunities in point-of-care testing to guide the development of emerging technologies
- Developing infrastructure to create multidisciplinary research collaborations that facilitate clinical testing early in the development process
- Validating results from point-of-care technologies
- Developing user-friendly devices
- Proving that point-of-care testing provides a clinical benefit over analysis at a central laboratory

Large-Scale Collaborative Activities

Multidisciplinary teams are essential to solving the complex problems that many emerging fields present. NIH-supported investigators in the promising field of tissue engineering and regenerative medicine, for instance, draw on the expertise of chemists, physicists, biologists, engineers, and computer scientists, among others. Coordinated efforts among these different groups are vital to continue progress made over the last two decades that has included fabrication of the first artificial organs. To make engineered tissue a viable clinical option, new computer programs must be designed to model the tissue in three dimensions. Novel approaches to fabrication and manufacturing are also needed for widespread use.

In an effort to develop new collaborations, NIH has implemented the Partnerships to Promote Innovation program. Examples of activities supported through this program include a cooperative research and development agreement, under which NIH and Siemens Medical Solutions will design new MRI technologies to diagnose and treat heart disease. Another agreement between NIH and the German National Research Center for the Environment will enable key genetic mouse models to be transferred to NIH investigators from the German Gene Trap Consortium.

The Biomedical Technology Research Resources (BTRRs) programs supported by NIH serve a unique purpose in the broad context of NIH-funded research. They represent a critical mass of technological and intellectual resources with a strong focus on service and training for outside investigators. They develop new technologies and tools in areas including imaging, informatics, synchrotrons, electron microscopy, proteomics and glycomics, optics, and lasers. Access to these technologies is critical to enabling research because they are frequently too advanced or expensive to be widely available. There are approximately 50 BTRRs located throughout the country that disseminate and promote the application of cutting-edge technologies they have developed across the full spectrum from bench to bedside. These centers are multidisciplinary and collaborative, and serve as catalysts for integrating the diverse efforts of NIH-supported researchers, providing technological infrastructure, experimental and computational resources, and expertise.

The goal of the NIH-funded Biomedical Informatics Research Network (BIRN) is to allow researchers to collaborate by sharing data and tools. The BIRN is developing the informatics infrastructure necessary to allow any group of investigators to share data among themselves or with a broader community (see also the section on *Disease Registries and Other Data Systems* in Chapter 3). The resulting collaborative environment extends beyond the boundaries of individual laboratories to enable collaborations that cross geographic and disciplinary boundaries.

Basic and clinical investigators are able to share disparate data as well as powerful new analytical tools and software across animal models and among multiple sites. This major initiative initially was developed to allow neuroimagers to share data and tools, but the infrastructure is generic and therefore applicable to other disciplines. With the infrastructure in place and the lessons learned from the neurology projects, NIH has just released a set of program announcements to expand BIRN to support other large-scale, collaborative investigations.

Transforming Health Care

The combination of new tools and techniques developed to improve basic research as well as those aimed at delivering better health care will transform the current medical paradigm into one that is predictive, personalized, preemptive, and participatory. These new tools and techniques are critical as the population ages and chronic, rather than acute, conditions become the norm.

NIH-supported researchers are leading the way toward a new paradigm in which technology is a central feature of fast and effective health care delivery. NIH funding of technology development provides an environment that enables investigators to think beyond what is conventional, to do so across disciplines, and to take the health care system to a level that will engage scientists, patients, and physicians in a collaborative experience.

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

Toward a New Era in Medicine

Pediatric Circulatory Support: Options for the circulatory support of pediatric patients younger than 5 years 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 2: *Chronic Diseases and Organ Systems.*
- (E) (NHLBI)

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 a cochlear implant. In the United States, roughly 22,000 adults and nearly 15,000 children have received one. 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 a cochlear implant at a young age develop language skills at a rate comparable to children with normal hearing. NIH-supported scientists found that the benefits of the cochlear implant far outweigh its costs in children. 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 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (NIDCD)

Hearing Aids and Directional Microphones: Approximately 32.5 million American adults report some degree of hearing loss (NCHS/NHIS data for 2003). 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 their aids. 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 to use 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 2: *Neuroscience and Disorders of the Nervous System*
- (E) (NIDCD) (GPRA Goal)

Gene Sequencing and Beyond

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 catalogue, 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 2: *Cancer* and Chapter 3: *Genomics*.
- (E/I) (**NCI**, NHGRI)

ENCODE: The ENCyclopedia *O*f DNA Elements (ENCODE) is an international research consortium organized by NIH that seeks to identify all functional elements in the human genome. The initial 4-year pilot phase has just been completed, and the consortium has published a series of papers describing an intricate network in which genes and other regulatory mechanisms interact in complex ways. Other insights include the discovery that the majority of DNA in the human genome is transcribed into functional molecules, called RNA, and that these transcripts extensively overlap one another. These findings challenge long-held beliefs that the genome has small sets of

genes and vast amounts of “junk” or untranscribed DNA. Until now, most studies have concentrated on the functional elements of specific genes, and have not provided information about functional elements in the vast majority of the genome that does not contain genes. ENCODE's exciting discoveries may well reshape the way scientists think about the genome and pave the way for more effective approaches to both understanding and improving human health.

- The ENCODE Project Consortium, et al. *Nature* 2007;447:799-816, PMID: 17571346
- For more information, see http://www.genome.gov/10005107
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NHGRI)

Genome Technology and the $1,000 and $100,000 Genome Initiatives: DNA sequencing spells out the order in which our chemical building blocks are arranged, making DNA sequencing a powerful resource for biomedical research. Although DNA sequencing costs have dropped by more than three orders of magnitude since the start of the Human Genome Project, sequencing an individual's complete genome for medical purposes is still prohibitively expensive. Developing technology to make whole-genome sequencing more affordable would enable the sequencing of individual genomes to become part of routine medical care. The Genome Technology program supports research to develop new methods, technologies, and instruments to rapidly and at low cost:

- Transcribe DNA sequences
- Check sequences for genetic variations (SNP genotyping)
- Aid research to understand the effects of genetic variations on genomic function.

Additionally, NHGRI supports two types of sequencing grants: (1) “Near-Term Development for Genome Sequencing” grants support research aimed at sequencing a human-sized genome at 100 times lower cost than is possible today ($100,000) and (2) “Revolutionary Genome Sequencing Technologies” grants aim to develop breakthrough technologies that will enable a human-sized genome to be sequenced for $1,000 or less. Currently, only analyses of ~ 500,000 Single Nucleotide Polymorphisms (SNPs) are being performed commercially at this cost; an individual's complete genome sequence (~ 3 billion base pairs) would offer vastly more information.

- For more information, see http://www.genome.gov/10000368
- For more information, see http://www.genome.gov/19518500
- This example also appears in Chapter 3: *Genomics*.
- (E) (NHGRI)

Large-Scale Sequencing Program: NIH's Large-scale Sequencing Program funds three major research centers in the United States to conduct genetic sequencing. During and since the completion of the Human Genome Project, NIH-funded centers have used their industrial-scale enterprises to improve DNA sequencing methods, thereby substantially decreasing costs and increasing capacity. For many years, the Program has achieved twofold decreases in cost approximately every 20 months. One of the main projects now under way is the sequencing of the genomes of other primates, such as orangutan, baboon, gibbon, and marmoset (in addition to chimpanzee and macaque, which are complete). By comparing the human genome to that of other primates, researchers can find important information about both health and abilities that are uniquely human and those shared with other species. The Program also supports the genomic sequencing of human pathogens (organisms that cause disease in humans) and their vectors, the organisms that carry those pathogens. Also, many mammals are being sequenced to identify elements that are functionally important to human biology. These studies will undoubtedly unveil new biological insights to increase our understanding of how the human genome works.

- Rhesus Macaque Genome Sequencing and Analysis Consortium, et al. *Science* 2007; 316:222-34, PMID: 17431167
- For more information, see http://www.genome.gov/10001691
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Sciences*.

- (E) (NHGRI)

Population Genomics, GAIN, and GEI: In February 2006, the U.S. Department of Health and Human Services 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, Foundation for the NIH, Pfizer, Affymetrix, Perlegen, 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 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 another approximately 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, http://www.genome.gov/19518663
- For more information, see http://genesandenvironment.nih.gov/, http://www.genome.gov/11511175
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*.
- (E/I) (NHGRI)

Probing Proteins

NIGMS/NCI Collaborative Access Team (GM/CA-CAT): Structural biology is a field in which scientists learn about molecules by determining their three-dimensional structures in atom-by-atom detail. Enormous facilities called synchrotrons allow researchers to use x rays to determine molecular structures more easily, quickly, and cheaply than ever before. Two NIH institutes (NIGMS and NCI) funded the development of a new section of the synchrotron at Argonne National Laboratory (the Advanced Photon Source). The new section includes three stations (beamlines) that scientists from across the United States will be able to use to determine the detailed, three-dimensional structures of molecules. This sort of research is important to understanding basic biological processes and designing drugs. The facility was to be in full operation in the last quarter of 2007.

- For more information, see http://www.nigms.nih.gov/Initiatives/PSI/
- (E) (**NIGMS**, NCI)

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 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 2: *Cancer* and Chapter 3: *Genomics*.
- (E/I) (NCI)

Protein Structure Initiative: Scientists learn a lot by studying the detailed, three-dimensional structures of proteins. This knowledge helps them better understand the biochemical processes involved in health and disease. It can also greatly advance the design of medicines to treat a wide range of diseases. Recognizing this, NIGMS established the Protein Structure Initiative (PSI) in 2000. This multimillion dollar initiative involves hundreds of scientists across the Nation and is a collaborative effort between the Federal government, universities, and industries. Already, members of the PSI have determined thousands of structures and have developed new

technologies that improve the speed and ease of determining molecular structures. In addition to benefiting the PSI team, this work has accelerated research in other fields.

- For more information, see http://www.nigms.nih.gov/Initiatives/PSI/
- (E) (**NIGM**S)

Membrane Protein Production and Structure Determination: The NIH Roadmap on Structural Biology seeks to develop innovative approaches and technologies for rapidly producing membrane proteins—the proteins tightly wedged within the lining of our cells. These protein samples can then be used to determine the proteins' underlying structures which will help researchers clarify the role of proteins in health and disease. Scientists currently have enormous difficulty pulling membrane proteins from cells in a condition suitable for functional and structural studies. Although these challenging proteins account for about 30 percent of all cellular proteins and are targets of 60-70 percent of known drugs, only about 100 structures of membrane proteins have been identified. In contrast, over 20,000 soluble protein structures have been determined. With the development of efficient protein-producing methods, researchers will be able to study and understand how membrane proteins function and interact with microbes, viruses, other cells, and drugs. By shifting the emphasis from hypothesis-driven research to technology development, the NIH Roadmap on Structural Biology has significantly impacted the membrane protein community. It has initiated collaborations among chemists, cell biologists, biophysicists, modelers, and physicists. Ultimately, the research will expand our knowledge of membrane protein structures, which may lead to improvements in drug design.

- For more information, see http://nihroadmap.nih.gov/structuralbiology/
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-003.html
- (E) (Roadmap—all ICs participate)

Insights From Animal Models

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 synch with the split-second pace of real-time neuronal activity. The novel technique borrows genes form 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 2: *Neuroscience and Disorders of the Nervous System*.
- (E) (**NIDA**, NIMH)

The Knockout Mouse Project (KOMP): The NIH Knockout Mouse Project (KOMP) is an NIH-wide effort to create a publicly available resource of knockout mouse mutations that can be used to study human disease. Knockout mice are strains of mice in which specific genes have been completely disrupted, or knocked out. By studying these mice, researchers can evaluate the effect of this systematic disruption of different genes on physiology and

development. Understanding the effects of gene disruption in mice will provide powerful tools to develop better models of inherited human disease. NIH has awarded 5-year cooperative agreements for the creation of knockout mice lines to Regeneron Pharmaceuticals Inc. to a collaborative team from Children's Hospital Oakland Research Institute, and to the Wellcome Trust Sanger Institute in England. NIH has also recently awarded $4.8 million to the University of California, Davis, and the Children's Hospital Oakland Research Institute to establish and support a repository for the KOMP. The repository will enable many more researchers to have access to the knockout mice and will ensure product quality for the 8,500 types of knockout mice currently available.

- Austin CP, et al. *Nat Genet* 2004;36:921-4, PMID: 15340423
- For more information, see www.komp.org
- This example also appears in Chapter 3: *Genomics*.
- (E/I) (NHGRI)

Multimodal PET and MRI Imaging Instrumentation: Investigators are developing a small animal PET/MRI system to study diseases such as cancer using animal models. This project will exploit the strengths of two widely used medical imaging modalities—positron emission tomography (PET) and magnetic resonance imaging (MRI). PET is a highly sensitive nuclear medicine imaging modality but requires radionucleotides and has poor spatial resolution. On the other hand, MRI has poor sensitivity but provides high spatial resolution and does not require radionucleotides. One expected application of the small animal PET/MRI system would be to develop imaging biomarkers for cancer. These biomarkers could provide new ways to monitor and test novel therapeutics, which may improve health care for cancer patients.

- Catana C, et al. *J Nucl Med* 2006;47:1968-76, PMID: 17138739
- For more information, see http://atlasserv.caltech.edu/~petmri/
- (E) (**NIBIB**)

Imaging Biological Systems

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 precancer, (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 2: *Cancer*.
- (E/I) (NCI)

Imaging Initiative From Molecules to Cells: Much human suffering is caused by the breakdown of the intricate and highly dynamic organization of the body at every level, starting with the structure of macromolecules such as proteins, progressing through ensembles of proteins that make molecular machines, to the sets of these machines that form organelles (mini-organs within cells), right up through cells and tissues. To make progress in fighting these diseases, we need to make progress in learning exactly how a pathogen, cancer cell, or faulty gene disorganizes living matter. The time is now ripe to turn the powerful new imaging approaches developed in physics and biophysics laboratories to the imaging of living material in health and disease, because then we can see exactly how things work and what goes wrong. IC intramural program leaders have collaboratively developed a strategic plan for trans-NIH efforts to realize the full potential of these powerful technologies for biomedical research. All of the NIH Institutes will play a role in moving forward on this plan, with leadership from the NIBIB, NICHD, and NCI.

- (I) (**NIBIB**, NCI, NICHD)

Molecular Imaging of G-Protein Coupled Receptors for Drug Development: What do over 50 percent of all therapeutic drugs have in common? They act on a specific type of receptor on the surface of cells known as the G-protein coupled receptor (GPRC). GPCRs form a large family of membrane-bound proteins containing seven trans-membrane helices connecting an extracellular receptor site to an intracellular G-protein binding site. This transmembrane nature provides extracellular control over important intracellular functions. To date, all of the drugs that target GPCRs have been developed using screening approaches. These approaches have been effective but their cumbersome and expensive nature severely limits widespread development of novel GPCR-targeted drugs for cancer, heart disease, obesity, and many other illnesses. Novel "structure-based" methods can overcome these problems and have been very successful with HIV protease inhibitors. However, structure-based drug design methods have not been possible with GPCRs because of the complexity of the structure and the fact that it sits within the cell membrane. NIH-funded researchers are developing and extending novel "solid-state" NMR technology to design new approaches that can obtain "atomic resolution" three-dimensional structures of GPCRs in their natural environment of the cell membrane. This new approach to drug design may substantially increase the rate of development of specific GPCR-targeted drugs.

- Park SH, et al. *J Am Chem* Soc 2006;128:7402-3, PMID: 16756269
- Nevzorov AA, et al. *J Biomol NMR* 2007;37:113-6, PMID: 17216304
- For more information, see http://nmrresource.ucsd.edu/facility/index.html
- For more information, see http://www.nibib.nih.gov/Research/ResourceCenters/Listname/Opella
- (E) (NIBIB)

New Light Microscope: By blending emerging advances in physics and microbiology, NIH researchers developed a new light microscope that allows scientists for the first time to visualize and determine how proteins are arranged and compose individual structures within a cell. Known as photoactivated localization microscopy, or PALM, the new technique enables researchers to better view cell structures and understand the complexity of proteins, the cells' building blocks. For example, using PALM, researchers could study several cellular subsystems, including those that provide energy for the cell's activities. In addition, researchers could visualize the distribution of the proteins involved in the assembly and budding of the AIDS virus from a host cell, literally giving scientists new insights into targets to stop viral replication.

- Betzig E et al. *Science* 2006;313:1642-5, PMID: 16902090
- For more information, see http://www.nichd.nih.gov/news/releases/microscope_view_protein.cfm
- (I) (**NICHD**)

Visualizing Transcription of Genes in Living Cells: Most genes serve one main purpose: as recipes for the body's proteins. The first step in using genes to produce proteins is called transcription. Although scientists think they know how transcription works, it has not been well studied in real-time in living cells. Now, NIH-supported researchers have developed fluorescent dyes and new techniques in microscopy that will enable them to watch transcription from individual genes. Faulty gene transcription can lead to cancer, so a detailed understanding of the process may lead to new ways to treat disease.

- Yao J, et al. *Nature* 2006;442:1050-3, PMID: 16929308
- For more information, see http://www.nature.com/nature/journal/v442/n7106/extref/nature05025-s3.mov
- (E) (NIGMS)

Image-Guided Interventions

Development of Image-Guided Interventions: Image-guided interventions (IGI) provide therapy that can minimize trauma and improve patient outcomes. They are applicable in procedures such as biopsy, surgery, radiation treatment, vascular interventions, and guidance during delivery of devices, drugs, cells, or genes. These improved capabilities are particularly important in light of the shifting trend in medicine toward a model of early, presymptomatic detection of disease. The need to support research and development in this area has been

identified at multiple workshops sponsored by NIH and other Federal agencies. In response, in August 2006, NIH issued a request for applications to support the first phase of a two-phase project that will deliver high-impact IGIs. Multidisciplinary collaborations and partnerships with industry were encouraged, with the goal of developing multipotential technologies with high clinical impact applicable across a range of diseases and disorders.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-06-003.html
- (E) (**NIBIB**, NCI) (GPRA Goal)

Diagnostics and Point-of-Care Technologies

Diabetes Research in Children Network (DirecNet): The risk of hypoglycemia is now the main obstacle to successfully managing type 1 diabetes mellitus (T1DM) 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 T1DM 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 T1DM 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: *Life Stages, Human Development, and Rehabilitation.*
- (E) (**NICHD**, NIDDK, NINDS)

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. Remove the light, and 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, while 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 2: *Cancer* and Chapter 3: *Clinical and Translational Research.*
- (E) (NIDCR)

Salivary Diagnostics: NIH stands at the forefront of efforts to develop salivary diagnostics, the use of saliva as a robust, sensitive, reliable, low-cost, user-friendly "point of care" mechanism for early disease diagnosis, monitoring drug levels, and detecting environmental insults. Salivary tests can be performed on the spot and require no painful needle sticks. A number of grantees are currently working to develop a tiny automated machine that can precisely measure levels of the various antibodies, antigens, and nucleic acids present in saliva. Recently, the promise of salivary diagnostics moved closer to becoming technologically feasible with the fabrication of the first disposable, low-cost miniaturized diagnostic platform to process small amounts of saliva, amplify its DNA, and detect the levels of DNA sequences of interest. Once development of a similarly robust sample preparation process is complete, the cassette will offer the first fully integrated, highly flexible platform for multiple analysis paths.

- Wang J, et al. *Lab Chip* 2006;6:46-53, PMID: 16372068

- (E) (NIDCR)

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 the genetic predispositions underlying diseases like addiction. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases using custom screening tools known as "gene chips" (e.g., the *neurexin* gene has been found to play a role in drug addiction). 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 of not only vulnerability to addiction and its frequent comorbidities, but also 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 *epi*genetics, 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, 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 2: *Neuroscience and Disorders of the Nervous System.*
- (E/I) (**NIDA**, NCI, NIAAA, NIMH) (GPRA Goal)

Exposure Biology Program of the GEI: As a major partner in the Genes, Environment, and Health Initiative within NIH, NIEHS has especially focused on the Exposure Biology/Exposure Measurement dimension of this initiative, through which we will improve the technologies for detection and measurement of the actual exposures sustained by human or other organisms that are currently often weak and imprecise. This is in contrast to the robust tools employed in the fields of genetics and genomics. Personalized measures of environmental exposure must be developed that are equivalent to the ability to measure genetic variability between individuals. The increasing sophistication of our understanding of the biological pathways involved in host response to a given exposure points the way toward the use of that knowledge to develop improved methods for detecting and measuring environmental exposures. Needed are relatively inexpensive, highly portable monitors—a wristband, watch, phone, or lightweight tote for example - that could accurately collect and retain large amounts of data on exposures and to some degree process that data into useful form. Recent advances in environmental and biological sensors suggest that the technologies are at hand, or can be readily engineered to provide precise measure of chemical and biological hazards at the point of contact and/or to characterize the biological fingerprint left by a class of environmental stressors. The value of these technologies would far exceed even the ingenuity required to create them, in enabling researchers to detect associations between environmental exposures and disease.

- For more information, see http://www.gei.nih.gov/exposurebiology/index.asp
- (E) (NIEHS) (GPRA Goal)

Alcohol Biosensors Program: This Advanced Research Program, modeled on the U.S. Department of Defense'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 will likely make their way to market in the next few years.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems.*
- (E) (NIAAA)

Point-of-Care Research Network: The need to improve the quality and accessibility of care while reducing costs is a significant challenge currently faced by the Nation's health care system. Adding to this challenge is the need to reduce health disparities and provide care for an aging population. Significant improvements in health care delivery can be achieved through the development of point-of-care systems that can be integrated into the health care delivery system through information and communications technologies. A major challenge in this effort is to evaluate the clinical feasibility of integrated technology in sensors, microsystems, imaging, and informatics. To address this challenge, NIH is establishing a Research Network that will develop integrated systems that address unmet clinical needs in point-of-care testing. This will be accomplished through the creation of multidisciplinary partnerships that will interact across the network to enable broad coverage of clinical and technological issues in point-of-care testing.

- For more information, see http://www.nibib.nih.gov/NewsEvents/SympReports/2006Apr11
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-06-002.html
- (E) (**NIBIB**)

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 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (**NICHD**, NIDCD, NIDDK)

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 over 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 PDAs 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 2: *Infectious Diseases and Biodefense.*
- (I) (NLM)

Genes, Environment, and Health Initiative, Exposure Biology Program: This trans-NIH initiative supports the development of environmental sensors for measurement of chemicals, dietary intake, physical activity, psychosocial stressors, and addictive substances and of “fingerprints” (markers) of biological response to exposures to these environmental factors. These new methods will ultimately be used to monitor environmental exposures that interact with genetic variations that influence health and disease. In addition, a workshop on measuring psychosocial stress and the social environment is planned for early FY 2008.

- For more information, see http://www.gei.nih.gov/exposurebiology/
- (E) (OD)

Large-Scale Collaborative Activities

Partnerships to Promote Innovation: NIH has implemented new collaborations with electronics and pharmaceutical industry leaders and with the German government to develop innovative technologies and their application to biomedical research. A Cooperative Research and Development Agreement (CRADA) between NIH and Siemens Medical Solutions has been adopted to promote the design of new magnetic resonance imaging methods for the diagnosis and treatment of heart disease. A material transfer agreement between NIH and the German National Research Center for the Environment is being negotiated to facilitate the transfer of important mouse genetic models from the German Gene Trap Consortium mouse distribution facility to NIH investigators. Additionally, a Materials-CRADA has been negotiated between NIH and Merck & Co. to facilitate transfer of proprietary Merck biologics and compounds for internal NIH research and development, with the specific aims of reducing transaction costs and getting necessary research materials into the hands of NIH investigators quickly and efficiently.

- Kellman P, et al. *Magn Reson Med* 2005;53:194-200, PMID: 15690519
- For more information, see http://tikus.gsf.de
- (I) (NHLBI)

Innovative Technologies for Engineering Small Blood Vessels: NIH has initiated a program of basic research studies to enlighten 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 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NHLBI)

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 whether these drugs are effective at killing malignant cells. Nanotechnology will likely change the very foundations of cancer diagnosis, treatment, and prevention.

- For more information, visit http://nano.cancer.gov/
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research.*
- (E/I) (NCI)

Biomedical Informatics Research Network (BIRN): Modern biomedical research generates vast amounts of diverse and complex data. Increasingly, these data are acquired in digital form, allowing sophisticated and powerful computational and informatics tools to help scientists organize, store, query, mine, analyze, view, and, in general, make better use and sense of their data. Moreover, the digital form of these data and tools makes it possible for them to be easily and widely shared across the research community at large. NIH has supported development of the BIRN infrastructure to share data and tools by federating new software tools or using the infrastructure to federate significant datasets. BIRN fosters large-scale collaborations by utilizing the capabilities of the emerging

national cyberinfrastructure. The project includes a Coordinating Center at the University of California, San Diego, which serves the critical task of developing, deploying, and maintaining key infrastructure components, including high-bandwidth connectivity, grid-based security, file management and computational services, techniques to federate databases, and shared visualization and analysis environments.

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

Biomedical Technology Research Resources (BTRRs): The BTRRs develop versatile new technologies and methods that help researchers who are studying virtually every human disease, each creating innovative technologies in one of five broad areas: informatics and computation, optics and spectroscopy, imaging, structural biology, and systems biology. This is accomplished through a synergistic interaction of technical and biomedical expertise, both within the Resources and through intensive collaborations with other leading laboratories. The BTRRs are used annually by nearly 5,000 scientists from across the United States and beyond, representing over $700 million of NIH funding for 22 institutes and centers. As an example, optical technologies enable researchers to:

- Harness the power of light to "see" biological objects, from single molecules to cells and tissues, which are otherwise invisible. New technologies using fluorescence and infrared spectroscopies revealed exquisite details of how proteins fold and interact.

- Detect and assess malignancy in a rapid, noninvasive manner. Optical technologies have been used successfully to measure responses of breast tumors to chemotherapy and define the margin of tumors so that surgeons can more precisely remove cancerous tissue during surgery.

- For more information, see http://www.ncrr.nih.gov/biomedical_technology/
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (**NCRR**)

Glycomics Technology Development, Basic Research, and Translation Into the Clinic: Complex carbohydrates are ubiquitous, found on the surfaces of cells and secreted proteins. Glycan binding proteins mediate cell signaling, recognition, adherence, and motility, and play a role in inflammation, arteriosclerosis, immune defects, neural development, and cancer metastasis. Detection and analysis of carbohydrate molecules are thus critical for basic and clinical research across the spectrum of health and disease, but widely regarded as among the most difficult challenges in biochemistry. Four NIH programs are striving to make this easier by working together across the domains of technology development and basic and translational research.

- Biomedical Technology Research Resources are developing and sharing cutting-edge technologies for analysis of carbohydrates in complex biological systems.

- Consortium for Functional Glycomics creates and provides access to technological infrastructure for carbohydrate biology and analysis in support of basic research.

- Alliance of Glycobiologists for Detection of Cancer and Cancer Risk leverages the technology and expertise developed in NIH programs for translational research in cancer biomarker discovery.

- A Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program funds the commercial development of innovative technologies for carbohydrate analysis.

- For more information, see http://www.ncrr.nih.gov/biomedical_technology/biomedical_technology_research_resources/technology_for_systems_biology/glycomics.asp

- For more information, see http://www.functionalglycomics.org/static/index.shtml
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (**NCRR**, NCI, NHLBI, NIGMS, NINDS)

Enabling Technologies in Tissue Engineering and Regenerative Medicine: Tissue engineering and regenerative medicine are interdisciplinary fields in which basic science aimed at understanding the cellular machinery combines with computational and engineering processes to control and direct the aggregate behavior of cells to form tissues and organs. While much progress has been made over the 20 or so years since the field first started, key technologies such as technology to rapidly expand, direct (along a specific cell line path), preserve, and track cells are not yet in place to accelerate development on all fronts. A program announcement sponsored by NIH, the National Science Foundation, and the National Institute of Standards and Technology was issued in 2006 and is focused on developing new infrastructural tools for the field. The funding opportunity will be open through FY 2008 in order to attract the best and most innovative ideas and research plans to advance the field.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-06-504.html
- (E) (**NIBIB**, NHLBI, NIAMS, NICHD, NIDCD, NIDCR)

National Centers for Biomedical Computing (NCBCs): The NIH Roadmap Bioinformatics and Computational Biology initiative provides a networked national effort to build computational tools and infrastructure for biomedical computing. The centers are devoted to all facets of biomedical computing, from basic research in computational science to providing the tools and resources that biomedical, clinical, and behavioral researchers need to do their work. The seven centers currently supported by the NIH Roadmap have made substantial progress in software development, data resources, and scientific ontologies. These advances are currently being used by the research community for studying a broad range of biological problems including cerebral palsy, autism, diabetes, asthma, Alzheimer's disease, Huntington's disease, schizophrenia, bipolar disorder, HIV/AIDS, and prostate cancer. The long-term goal of the initiative is to create a national software engineering system that will enable biomedical and clinical researchers to share and analyze data using a common set of software tools.

- For more information, see http://nihroadmap.nih.gov/bioinformatics/
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems.*
- (E) (Roadmap—all ICs participate)

Transforming Health Care

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 man-made reversible adhesive. It is envisioned that the new adhesive will be used for many medical applications including enhancing the retention of oral/maxillofacial prosthetics.

- Lee H, et al. *Nature* 2007;448:338-41, PMID: 1763766
- 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 2: *Life Stages, Human Development,*

and Rehabilitation.

- (E) (NIDCR)

Suture Developed Using DNA Technology: Supported by an SBIR award, scientists at Tepha, Inc., have developed a new, bioabsorbable surgical suture that is stronger, more flexible, and capable of retaining its strength longer than existing absorbable sutures. The scientists created the suture material in a new way, by genetically engineering bacteria to produce it for them. In February 2007, the FDA approved Tepha's ability to market the sutures. The company hopes that, in the future, the same material will be used for other medical devices, like surgical meshes for hernia repair, artificial heart valves, absorbable stents, and devices to repair and replace ligaments and tendons.

- For more information, see http://www.tepha.com/publications/media.htm?ident=21
- (E) (NIGMS)

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 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (**NINDS**, NIBIB, NIDCD, NICHD, NEI)

The Cancer Biomedical Informatics Grid™ (caBIG): The caBIG initiative has been launched to accelerate research discoveries and improve patient outcomes by linking researchers, physicians, and patients throughout the cancer community. caBIGTM completed its 3-year pilot project in March 2007. This date represents a new phase of evolution, as NIH is committed to bringing caBIGTM 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 2: *Cancer*.
- (E/I) (NCI)

Shared Instrumentation Grant and High-End Instrumentation Programs: The goal of the NIH instrumentation programs is to provide new-generation technologies to groups of NIH-supported investigators for a broad array of basic, translational, and clinical research. These programs provide essential instruments that are too expensive to be obtained through regular research grants. The Shared Instrumentation Grant (SIG) program funds equipment in the $100,000-$500,000 range, while the High-End Instrumentation (HEI) program funds instrumentation in the $750,000-$2 million range. New research technologies supported by these programs enable novel modes of inquiry, which in turn lead to increases in knowledge, and ultimately have the potential for improving human health. To increase cost-effectiveness, the instruments are located on core facilities with trained technical staff to assist in protocol development and to facilitate integration of new technologies into basic and translational

research. In FY 2006 and 2007 the SIG program funded a total of 264 grants for $95.2 million; the HEI funded a total of 39 awards for $55.9 million.

- For more information, see http://www.ncrr.nih.gov/biomedical_technology/shared_instrumentation/
- This example also appears in Chapter 3: *Clinical and Translational Research* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NCRR)

Analytical Methods and Reference Materials (AMRM) Program: The rapid expansion of the dietary supplement marketplace has resulted in a proliferation of ingredients and products and overtaken the pace of development of reliable analytical methods. Precise, accurate, and rugged analytical methods and reference materials are essential for verification of ingredient identity and measuring the amounts of declared ingredients in raw materials and finished products. Also, dietary supplement labels are required to list certain facts about product identity and content and to be truthful and not misleading. For example, a dietary supplement that boasts "500 mg of Vitamin C from rosehips per tablet" on its label should be expected to contain both 500 mg of Vitamin C and rosehips. That this is not always the case is due in part to the lack of proven and agreed-upon methods to precisely assess the quantity of constituents of many supplements and supplement ingredients. NIH's AMRM program is intended to assist in providing these critical tools for quality assurance. The program promotes development, validation, and dissemination of analytical methods and reference materials for commonly used dietary supplement ingredients. An external panel of experts recently reviewed the Program and found that it had substantially raised the awareness of the need for better quality-control measures within the dietary supplement community and provided research funding crucial for development, validation, and dissemination of reference materials and analytical methods.

- For more information, see http://dietary-supplements.info.nih.gov/Research/Analytical_Methods_and_Reference_Materials_Program.aspx
- (E) (ODS)

Evidence-Based Review Program: In FY 2001, congressional appropriations report language included text asking that NIH review the current scientific evidence on the efficacy and safety of dietary supplements and identify research needs. In response, NIH established an evidence-based review program using the Evidence-based Practice Centers Program established by the Agency for Healthcare Research and Quality to conduct systematic reviews of the scientific literature and prepare reports of their findings. These reports have resulted in the publication of a number of articles in the peer-reviewed literature, and have helped NIH make decisions on research priorities in these areas. NIH institutes and centers have found these reports invaluable in presenting what is and is not known in a research area, thus laying a sound foundation for identifying gaps in knowledge and providing a strong scientific basis for the development of a research agenda. Currently, NIH is sponsoring an evidence report on *Effectiveness and Safety of Vitamin D* that will be used to establish a research agenda to answer important public health questions about vitamin D, and as the basis of a conference planned for September 2007 with the goal of presenting a balanced overview of the available evidence on the efficacy and safety of vitamin D as an update to the 2003 NIH Conference on Vitamin D and Bone Health.

- For more information, see http://vitamindandhealth.od.nih.gov/
- For more information, see http://ods.od.nih.gov/Research/EvidenceReports.aspx
- (E) (ODS)

Multidisciplinary and Interdisciplinary Research

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 trans-dermal vaccine patch that could be rapidly distributed through pharmacies, fire stations, or the U.S. mail and self-administered in a painless manner by patients. 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 pandemic influenza response. This innovative application impacts the U.S. Department of Health and Human Services Pandemic Influenza Response and Preparedness Plan and NIH's directives on High Priority Influenza Research Areas.

- For more information, see http://www.hhs.gov/nvpo/pandemicplan
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense.*
- (E) (NIBIB)

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, mathematics, and computer science (e.g., computational biology). Equally important to our understanding of cancer is systems genetic research (systems biology + genetics). Networks of genes can be found and their associations tested and quantified, with parallel association studies on relevant human populations.

- For more information, see http://icbp.nci.nih.gov/
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (NCI)

Critical Issues in eHealth Research Conference: Toward Quality Patient Centered Care (September 2006): This second of two eHealth conferences served three purposes: (1) to highlight research methodologies that intersect across information technology, health communications, behavioral science, medical science, and patient care research, (2) to showcase existing and emerging technologies relevant to communications among patients and their health care teams, and (3) to discuss conceptual issues related to patient-centered eHealth research.

- Atienza AA, et al *Am J Prev Med* 2007;32:S71-4, PMID: 17466821
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (**OBSSR**, NCI, ODP/ORD)

Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences: Merging scientific insights and technologies gleaned from behavioral and social sciences with approaches from other scientific disciplines offers the promise of further advancing the public health mission of NIH. This NIH Roadmap initiative funds projects that develop new/innovative measures, methods, and technologies that support the integration of human social and/or behavioral science with other disciplines across varying levels of analysis.

- For more information, see http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp
- (E) (Roadmap—all ICs participate)

Nanomedicine Development Centers (NDC): The structures inside living cells operate at the nanoscale (about 1/10,000 the thickness of human hair). Recent advances in nanotechnology, which refers to the understanding and control of materials at the nanoscale, have yielded new tools to probe and manipulate objects at the nanoscale. These tools, as well as a variety of newly engineered nanostructures, are starting to be used in biomedical research. Nanomedicine, an offshoot of nanotechnology, is a rapidly emerging, multidisciplinary field that was identified as one of the nine initial NIH Roadmap initiatives. In late 2006, NIH completed the establishment of a national network of eight NDCs after an intensive 2-year planning and application process that involved extramural stakeholders from scientifically and medically diverse fields. The overarching goal of these centers is to understand and control the nanomachinery inside living cells in order to diagnose or treat disease and repair tissue. The work at these centers, which involve over 120 biomedical researchers located in 30 institutions, 12 States, and 6 countries, is geared toward understanding the fundamental properties of intracellular structures with great precision so that highly specific treatment or possibly even replacement of these structures can be achieved with

few or no side effects. Unlike traditional, translational research targeting a specific medical problem, these centers are beginning with basic science studies and, over a 10-year period, will apply their tools, technologies, and newly developed structures to a variety of disease or wound conditions that will be identified in parallel with, and as a consequence of, the technological developments. It is expected that this novel approach will stimulate the emergence of nanomedicine as a major contributor to improving human health in a variety of medical specialties.

- For more information, see http://nihroadmap.nih.gov/nanomedicine/index.asp
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences.*
- (E) (Roadmap—all ICs participate)

NIH Roadmap Interdisciplinary Methodology and Technology Summit: The purpose of this NIH Roadmap Summit (August 2006) was to identify opportunities for developing research methodologies and technologies at the intersection of behavioral and social sciences with other disciplines. Topics discussed at the meeting included the following: large complex datasets, multilevel approaches, intergenerational approaches, economics/econometrics, Geographical Information Systems and neighborhood data, ecological momentary assessment, and combining qualitative and quantitative methods.

- For more information, see http://nihroadmap.nih.gov/interdisciplinary/summit0806/
- (E) (Roadmap—all ICs participate)

Summary of Research Activities by Key Approach and Resource

Research Training and Career Development

For years the sense of smell had remained the most enigmatic of our senses. The basic principles for recognizing and remembering about 10,000 different odors were not understood. However, in 2004 Dr. Richard Axel and Dr. Linda Buck received the Nobel Prize in Physiology or Medicine for determining how the sense of smell or olfaction actually works. Their seminal discovery was that the mammalian genome contains a family of genes that make receptors for odorants. They also found that these receptors are located on olfactory receptor cells, which occupy a small area in the inner lining of the nose, where they bind odorant molecules and signal the brain that a smell has been detected. The NIH is particularly proud that Dr. Buck was awarded a Nobel Prize because, as she followed the long path to becoming a scientist, Dr. Buck was the recipient of a National Research Service Award fellowship, which supported her postdoctoral research training from 1980 to 1982, training that very likely contributed to solving the mystery of the sense of smell.

Introduction

Louis Pasteur wrote that "Chance favors the prepared mind." NIH research training and career development programs aim to prepare new minds for research and ensure that diverse pools of highly trained scientists are available in adequate numbers and with appropriate expertise to generate new discoveries, meet the needs of rapidly moving science, and address complex and evolving health care challenges. These critical means of building and maintaining research capacity are long-term investments that bring competitive advantage to the Nation as well as dividends in the form of renewed generations of investigators with novel and bright ideas. Training is where cures begin. This investment in "intellectual capital" provides the source of ideas for investigator-initiated research projects, which historically have been the primary engine for generating scientific breakthroughs. Each generation of scientists paves the way for the discoveries of the next generation; thus, it is critical to ensure that there is a continually reconstituted pool of highly trained investigators in the pipeline pursuing new knowledge and better therapies. NIH's research training and career development programs cover a broad range of basic biomedical, behavioral, and clinical research, including the interdisciplinary junctures among the fields.

By sponsoring training and career development programs in universities, teaching hospitals, NIH laboratories, and other research-intensive settings, NIH expects that trainees and newly trained investigators not only will be exposed to the latest research findings and techniques, but also will be prepared to rise to the challenge of emerging problems in medicine and health. To further ensure that the research workforce will be poised to respond to evolving public health needs, NIH takes steps to recruit future researchers from underserved and underrepresented populations; strengthen research capacity in developing countries from which health threats often originate; and encourage individuals to focus on targeted or underresearched areas (such as clinical and translational research, rare diseases, health disparities, and global health priorities).

Aligning the requisite expertise with public health needs is complicated by the evolving nature of biomedical, behavioral, and clinical research; the time required for research training; the international nature of research; and the global mobility of the research workforce. Preparing for a career in research generally requires a commitment of 8 to 12 years or more of predoctoral and postdoctoral training and career development, during which time science is advancing, new diseases are emerging, and existing diseases are becoming better understood, diagnosed, and prevented.

In determining how best to sustain the continuing need for biomedical and behavioral scientists, NIH is guided by regularly scheduled analyses of the research workforce. Chief among these assessments are recurring studies conducted by the National Academies, which provide guidance on the fields in which researchers are likely to be required and on the number of new investigators needed in the basic biomedical, behavioral, and clinical sciences. NIH also routinely evaluates the outcomes of its training programs, comparing the subsequent research involvement of students and postdoctoral scholars who participate in NIH research training with their counterparts who were trained through other channels. Beyond such agency-wide assessments, individual ICs determine the need for new scientific personnel in mission-specific research areas through targeted evaluations, input from extramural investigators, and guidance from their national advisory councils.

NIH offers a broad range of research training and career development opportunities in the extramural and intramural research communities, through institutional training awards and individual fellowships, individual and institutional career development awards, continuing education, workshops, research grants, and awards and supplements to promote diversity or reentry into health-related research careers. While its programs are largely directed toward graduate students and newly trained investigators, NIH offers a number of highly focused training and career development opportunities for individuals at other career stages, including college students and established scientists.

All NIH training and career development programs foster and encourage participation of a diverse population of subjects. NIH expects that efforts to diversify the scientific workforce will lead to the recruitment of the most talented researchers from all groups, improved quality of the educational and training environment, more balanced and broader perspectives in setting research priorities, enhanced ability to recruit subjects from diverse backgrounds into clinical research protocols, and improved capacity to address and eliminate health disparities. In addition to NIH's dedication to inclusion of minorities and other disadvantaged populations in the biomedical research workforce (see section on Minority Health and Health Disparities in Chapter 2), NIH also is committed to the recruitment, retention, reentry, and advancement of women in biomedical research careers. Perhaps the most visible recent NIH activity in this regard is the NIH Director's establishment of the NIH Working Group on Women in Biomedical Careers. This Working Group is examining the issues raised and the challenges posed by *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, a 2007 report from the National Academies. The report itself was stimulated by NIH hearings and a workshop. Now, with the report in hand, NIH is carefully considering its recommendations to government agencies on maximizing the potential of women scientists and will develop innovative strategies to advance women's careers.

Summary of NIH Activities

Extramural Programs and Progress: Research Training

Trans-NIH Programs and Initiatives

Training for a career in research typically requires a combination of specialized coursework and hands-on research experiences under the guidance of an established investigator. A majority of NIH-supported research training activities are focused on predoctoral students and postdoctoral scholars and are provided through institutional training grants (T awards) or individual fellowships (F awards). The principal NIH research training program for U.S. citizens and permanent residents, in size and breadth of coverage, is the Ruth L. Kirschstein National Research Service Award (NRSA) program. The goal of the NRSA program is to support promising students and postdoctoral scholars with the potential to become productive, independent investigators in fields relevant to NIH's mission. Training activities can be in basic biomedical or clinical sciences, in behavioral or social sciences, in health services research, or in any other discipline relevant to the NIH mission. All ICs with funding authority award NRSA institutional research training grants and fellowships, except FIC and NLM. Reflecting the unique nature of their missions, the latter two ICs have distinct training authorities, separate from the NRSA program. NIH also supports a

substantial amount of research training indirectly though its research grants. Though not an NIH "program" per se, the impact of this support is significant. Graduate students and recent postdoctoral scholars participating as research assistants gain knowledge, skills, and experience that help prepare them for careers in research.

Through the NIH-wide program of NRSA institutional training grants and fellowships, NIH ICs supported nearly 16,600 graduate students and postdoctoral scholars at universities, teaching hospitals, and research centers in nearly every State in FY 2006. Institutional training grants form the core of NIH's research training programs, providing support to more than 80 percent of all NRSA program participants. Training grants play a particularly important role at the predoctoral level: approximately three-fifths of trainees are graduate students, often engaged in coursework and laboratory rotations in preparation for identifying an area of research for focused study. (See Appendix D for a breakdown on the demographics of NRSA participants and a summary of the number and type of doctoral degrees awarded to predoctoral NRSA recipients.)

Individuals interested in research training in universities or departments where there are no institutional training grants, as well as advanced students and postdoctoral scholars seeking tailored training opportunities, have the option of applying directly to NIH for an individual research training fellowship. Slightly more than one-half of the NRSA fellowships in FY 2006 were awarded to postdoctoral scholars, providing recipients valuable experience in initiating and testing their own research ideas before becoming full-fledged investigators[16].

NRSA training grants and fellowships may target broad-based or field-specific research training, depending on the needs identified by the administering IC. In recent years, this flexibility has allowed the NRSA program to respond to interest in greater integration of training activities across NIH in order to fulfill workforce needs shared by multiple ICs. The result has been a series of trans-NIH research training initiatives through the NIH Roadmap for Medical Research and other channels.

At its inception in 2003, for example, the NIH Roadmap identified interdisciplinary and clinical research training as NIH-wide priorities and initiated new NRSA research training awards in these areas. The Roadmap Interdisciplinary Research Training Initiative, in particular, is designed to overcome disciplinary boundaries and broaden the knowledge base of future investigators so they might bring new insights and analytical approaches to health problems.

As the early Roadmap research training initiatives have matured, some have been selected for continuation and further expansion. One such former Roadmap initiative—a trans-NIH NRSA institutional research training grant in clinical and translational research—has now been incorporated as an option in every Clinical and Translational Science Award (CTSA). The CTSA program is an ambitious effort to spur the transformation of clinical and translational research in order to accelerate the development of new treatments. Creating multidisciplinary research teams that include physicians, basic scientists, statisticians, specially trained research nurses, informatics experts, and others is central to this transformation. The CTSA program will grow through 2012 to serve about 60 academic sites, providing research training and career development opportunities in areas such as clinical research design, epidemiology, biostatistics, pharmacology, biomedical informatics, behavioral science, and ethics to more than 1,200 NRSA trainees and new investigators. (CTSA trainees are included in the data provided in Appendix D.)

Efforts to coordinate research training in neuroscience preceded the NIH Roadmap by several years and provided an early model for addressing research training challenges across NIH. In 1997, a number of ICs announced that the Jointly Sponsored Predoctoral Training Program in the Neurosciences would support NRSA institutional training grants to provide broad neuroscience training for graduate students in the first and second years of study. This program has since become affiliated with the NIH Blueprint for Neuroscience Research, a framework that brings together the 16 NIH Institutes, Centers, and Offices that support neuroscience research and training, and provides a channel for coordinating their efforts. Other more recent Neuroscience Blueprint research training activities

[16] For more information, see http://report.nih.gov/NIH_Investment/PPT_sectionwise/NIH_Extramural_Data_Book/NEDB%20TRAINING_FELLOWSHIP.ppt

include initiatives to provide training in translational research relevant to neurobiology of disease, neuroimaging, computational neuroscience, and neurodegeneration. Many programs funded through these new initiatives will include special features to foster collaborative interdisciplinary relationships, such as cross-training basic and clinical researchers and providing dual mentors to every trainee, each with a different area of expertise.

To help ensure the diversity of the research workforce, NRSA training grants and fellowships include features designed to provide research training opportunities to individuals from populations and backgrounds typically underrepresented in research (see also the section on *Minority Health and Health Disparities* in Chapter 2). Consistent with Section 487(a)(4) of the PHS Act, NRSA policy requires institutional training grant directors to take steps to recruit and retain trainees from disadvantaged backgrounds (including racial and ethnic minorities). Through the Ruth L. Kirschstein NRSA Individual Predoctoral Fellowship (F31) to Promote Diversity in Health-Related Research, NIH supports biomedical and behavioral research training designed to result in the recruitment of individual graduate students from these backgrounds.

Part of the inherent challenge of recruiting talented individuals into graduate programs is to have a pool of competitive undergraduates from which to draw. The Minority Access to Research Careers (MARC) Undergraduate Student Training in Academic Research, Institutional NRSA Research Training Grant (T34) is intended to support undergraduate research training to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to the Nation's biomedical and behavioral research agenda. These are honors students majoring in the sciences who have an express interest in a biomedical research career and who intend to pursue postgraduate education leading to the Ph.D., M.D.-Ph.D., or other combined degree. To help program directors recruit suitable students for doctoral programs, the Community for Advanced Graduate Training was launched in 2007 to connect MARC undergraduate students with predoctoral research training grant programs. The MARC program is an institutional program and does not use race/ethnicity as a criterion for individuals supported by the program.

The relative diversity of NRSA participants reflects NIH's commitment to cultivating a broad-based scientific workforce. Among FY 2006 trainees and fellows who reported their race and ethnicity, 67 percent were White, 14.8 percent were Asian, 9.1 percent were African American, 6.5 percent were Hispanic, 1.1 percent were Native American, and 0.06 percent were Native Hawaiian or Pacific Islanders. Nearly 52 percent of NRSA trainees and fellows in FY 2006 were women[17].

IC Programs and Initiatives

Because each NIH IC has its own specific research agenda, individual ICs are responsible for specifying the need for scientists in their respective scientific fields, selecting individuals and institutions for NRSA or other research training awards to meet the needs identified, and reviewing annual progress toward building or enhancing capacity in the research workforce. Areas targeted for research training initiatives reflect the full array of IC funding interests, from basic research training in biology, biostatistics, dentistry, epidemiology, and population, to topics at the intersection of two or more fields. As an example, NIGMS promotes interdisciplinary, collaborative, and innovative research through 11 different predoctoral training areas of interest to the Institute. In July 2007, it funded the first two awards of a new institutional NRSA training grant program focused on Predoctoral Training at the Interface of the Behavioral and Biomedical Sciences. Several ICs support combined M.D./Ph.D. training, including NIGMS, which funds the Medical Scientist Training Program. This program supports exceptional students pursuing an integrated program of graduate training in the biomedical sciences and clinical training offered through medical schools.

Other current IC initiatives include research training programs in the areas of chemical biology of cancer; infectious diseases; complementary and alternative medicine; chemistry related to drug abuse and addiction; genomic analysis; human genes and the environment; reproductive, perinatal, and pediatric epidemiology; medical informatics; and interdisciplinary research; as well as fellowship opportunities in complementary and alternative

[17] For more information, see http://grants.nih.gov/grants/policy/sex_gender/q_a.htm#q13

medicine, nursing, orthopedic surgery, muscle disease, and embryonic stem cell research.

While focusing on and supporting activities that address their respective missions and disease areas, ICs follow NIH-wide guidelines for NRSA research training and frequently collaborate to sponsor specific initiatives where there are overlapping interests or to stimulate interest in emerging fields. For example, in January 2007, NIEHS and NHGRI jointly sponsored a new Human Genes and the Environment Training Program that seeks to build on the established foundations in exposure biology and high-throughput genomics, to produce a new generation of scientists who are equally at home in genomics and environmental health sciences and can seamlessly interact with investigators from both fields. This new cadre of scientists not only will be equipped to advance methodologies and technologies in environmental genomics/genetics, but also will be able to use these tools and resources to disentangle and evaluate the enormous number of environmental factors that directly influence or interact with genetic factors to cause disease.

NLM institutional training grants and fellowships generally parallel the structure and requirements of the NRSA program and reflect NLM's unique role as the primary federal sponsor of biomedical informatics research and training. Like the ICs that provide NRSA research training, NLM prepares the next generation of informatics researchers and health information specialists through both institutional grants (T15s) and fellowships (F37s). The institutional programs support graduate and postdoctoral training in a broad range of topics, including health care information, bioinformatics, systems biology, imaging informatics, and public health informatics. NLM's individual fellowship programs provide opportunities for librarians, scientists, health professionals, and others interested in serving as information-specialist members of professional teams, whether in clinical or basic biomedical research or related health fields. Unlike NRSA research training awards, some NLM training programs are open to master's degree holders seeking further graduate level coursework and hands-on training.

Reflecting the FIC mission to build research capacity in the developing world, FIC institutional training grants (D43s) differ from those offered by the NRSA program or by NLM by allowing a broader range of participants and emphasizing the development of institutional partnerships and collaborations between U.S. and international universities and scientists. Most FIC programs focus on providing research training to individuals from developing nations, but a number of selected programs provide opportunities to U.S. students and postdoctoral scholars interested in international health research. FIC training programs are contributing to the building of sustainable research capacity in the developing world to enhance prevention, treatment, and control of infectious diseases, including HIV/AIDS, TB, and malaria, which are major causes of morbidity and mortality in those regions. Other FIC programs target research training in the areas of clinical, operational, and health services research; noncommunicable diseases; population studies and reproductive biology; environmental and occupational health; trauma and injury; and informatics training for global health. In order to foster long-term scientific partnerships between U.S. and foreign investigators, most FIC training grants require a joint collaboration between an American and a foreign institution.

Strength From Partnerships

Research training involves collaboration between NIH and its grantee institutions in the form of shared responsibilities and funding. In making NRSA training grant awards, for example, NIH relies on universities and other sites that receive support to select the best trainees, determine the curriculum and other aspects of the training program, and provide mentorship and supplemental funding to participating students and postdoctoral trainees. Although NRSA fellowships are targeted to individual students or postdoctoral scholars, NIH expects the sponsoring institutions to provide fellows with experienced mentors and supplemental research funding support. In some targeted NRSA research training programs, NIH also partners with other agencies, private foundations, and professional societies to achieve shared research training goals.

Partnerships between NIH and the private sector are helping to accelerate research training in creative ways. In 2006, for example, NIH announced public-private partnerships with the American Skin Association and the Orthopaedic Research and Education Foundation to increase the number of dermatologists and orthopedic surgeons with research training in epidemiology, clinical trials, and outcomes research. The ultimate goal of these two research training initiatives is to enhance the workforce of trained investigators who can design and carry out

studies on the prevalence of skin diseases and bone conditions and hasten progress in their treatment by evaluating the effectiveness of therapeutic interventions. The fellowships resulting from this public-private partnership support up to 2 years of advanced training and provide approximately $30,000 in additional funds annually to supplement stipends or other research training expenses for each fellow.

NIH Training Program Evaluations and Assessments

Since the NRSA program was established in 1974, NIH training programs have been regularly reviewed and evaluated. The National Academies have undertaken regular reviews of the medical research workforce and made recommendations for modifications in the size and focus of the NRSA program. In addition, the NRSA program has undergone multiple independent outcome evaluations, has assessed its processes and outcomes against several Government Performance and Results Act (GPRA) goals, and recently completed a Program Assessment Rating Tool review by the White House Office of Management and Budget (OMB) with flying colors. These reviews have been coordinated by the NIH Office of Extramural Research (OER), which oversees the NRSA program. Increasingly, however, individual ICs also are undertaking evaluations of their specific NRSA and other research training programs.

National Academies Reviews. Over the past 30 years, the NRSA program has been the subject of more than a dozen studies by NAS, which have provided expert guidance on the fields in which researchers are likely to be required and on the number of new investigators needed in the basic biomedical, behavioral, and clinical sciences. The recurring nature of these studies ensures that NIH research training programs reflect changes in science and research needs that inevitably occur over time. In the early 1980s, for example, NIH reduced the size of the NRSA training program after committees of the National Academies concluded that the number of new scientists entering the research workforce exceeded the number of permanent research positions available. More recently, NIH has followed recommendations from National Academies committees for enhancing stipend levels, promoting the early completion of research training, and improving workforce data collection and analysis.

Members of the committee producing the most recent report from the National Academies, published in 2005, commended the NRSA program, noting "quality is an essential ingredient for progress. In this regard, the NRSA Program plays a unique role… [setting] the standards for the entire research training establishment. In addition, they attract high-quality students into research and into fields of particular need. The record of success of NRSA holders in obtaining research funding is impressive."[18]

Independent Outcome Evaluations of NRSA Training. Evaluations of the outcomes of NRSA research training routinely have found that graduate students participating in NRSA programs complete their degrees faster, are more likely to pursue research careers, and have greater subsequent success in research than do students not participating in NRSA programs[19],[20]. Similarly, a 2006 evaluation of NRSA postdoctoral training found that NRSA postdoctoral fellows were more likely to successfully pursue research careers. Over 32 percent of former NRSA postdoctoral fellows applied for and successfully received NIH research funding within 10 years of completing their training, compared to about 20 percent of other postdoctoral fellows[21].

Government Performance and Results Act (GPRA) Goals. Every year, NIH assesses NRSA research training outcomes and program management against two goals established under GPRA. In the first of these goals, NIH seeks to measure the quality of its programs and ensure that substantial numbers of trainees and fellows are retained in research careers, by comparing the proportion of former NRSA trainees and fellows that apply for and

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[18] For more information, see http://www.nap.edu/catalog.php?record_id=11275#toc

[19] For more information, see http://grants.nih.gov/training/career_progress/index.htm

[20] For more information, see http://www.nsf.gov/statistics/showsrvy.cfm?srvy_CatID=3&srvy_Seri=5

[21] For more information, see http://grants1.nih.gov/training/NRSA_report_5_16_06-2.doc

successfully receive NIH support against their peers. Subsequent NIH support reflects the impact of NRSA research training on the ability of trainees and fellows to successfully pursue and sustain a research career.

The second training-related GPRA goal measures NIH progress in improving the efficiency of NRSA program management by developing and implementing an electronic system for appointing trainees to institutional training grants. By 2012, NIH expects the new system to be fully implemented and that 100 percent of trainees will be appointed to training grants electronically rather than through paper appointment forms. The new system, known as xTrain, will be pilot-tested by nine institutions beginning in fall 2007. When available for general use, xTrain is expected to save substantial staff time and eliminate data entry errors, increasing NIH's efficiency and enhancing the integrity of NRSA data used for program monitoring and evaluation purposes[22].

Program Assessment Rating Tool Review. In 2006, NIH training and career development programs underwent a Program Assessment Rating Tool review and received the highest rating possible from OMB examiners. OMB judged the NIH Research Training and Career Development programs as "effective" in training and retaining researchers in the biomedical research field, recognized the programs for having successfully met ambitious long-term and annual goals, and praised NIH for its long tradition of independent evaluation.

Institute and Center Training Evaluations. In addition to scheduled NIH-wide assessments of the programs coordinated through OER, individual NIH ICs undertake periodic, targeted evaluations to improve implementation and assess outcomes of their own training programs. Institute-specific evaluations typically focus on research training needs in particular areas and are often conducted by independent "blue ribbon" panels of scientific leaders from around the country. For example, NCCAM convened an independent expert panel to evaluate its programs in light of the unique training needs of complementary and alternative medicine research[23]. Other ongoing IC assessments include evaluations of how effectively CTSA training grants foster pediatric and other clinical researchers and of the outcomes of the NIAMS research training (T32 and F32) programs.

Extramural Programs and Progress: Career Development

Given the pace at which science advances, novel techniques and methods are introduced, and new fields emerge, maintaining a vibrant workforce requires support for scientific talent to fully develop and stay up to date. NIH Career Development Awards (K awards) address that need[24]. Collectively, more than a dozen types of K awards support investigators as they establish their research careers, pursue new directions, or dedicate themselves to training and mentoring the next generation of scientists. Like the T and F training awards, some career development awards support institutional activities to nurture careers and others directly support individual development.

Many career development awards are designed for researchers at specific career stages, particularly newly trained investigators. The new NIH-wide Pathway to Independence Award accelerates the transition from mentored to independent research by providing a bridging mechanism. The initial 1- to 2-year mentored phase of the award allows investigators to complete their supervised research work, publish results, and search for an independent research position. The second, independent phase, allows awardees to establish their own research program and apply for independent research support. In addition, many ICs offer their own Career Transition Award to support new investigators as they make the move to faculty positions. Other "mentored" career development awards provide support for a sustained period of protected time for intensive research career development under the guidance of an experienced mentor, or sponsor. The expectation is that, with this experience, awardees will be able to take the final steps toward establishing independent research careers and becoming competitive for new

[22] NIH FY 2008 Performance Detail, pp. 275-76.

[23] For more information, see http://nccam.nih.gov/training/report.htm

[24] For more information, see http://grants.nih.gov/training/careerdevelopmentawards.htm

research project grant funding. For example, ORWH supports the Building Interdisciplinary Research Careers in Women's Health program, which pairs junior faculty with senior investigators in an interdisciplinary environment. At the other end of the career spectrum, a number of ICs provide Senior Scientist Research and Mentorship Awards. These awards provide salary support for outstanding senior scientists and recognized leaders so that, through an interval of protected time, they can focus intensively on their research and mentor new investigators.

Several career development awards foster the involvement of clinicians in research. The Mentored Clinical Scientist Research Career Development Award continues a long-standing NIH commitment to provide support and protected time to individuals with a clinical doctoral degree so that they can engage in an intensive, supervised research career development experience. The award supports both didactic study and mentored research for individuals with a wide variety of clinical degrees, including the M.D., D.D.S., D.V.M., and Pharm.D. A sister program, the Mentored Patient-Oriented Research Career Development Award, supports the career development of clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research.

Other career development programs target specific areas of science. Examples here include the Career Enhancement Award for Stem Cell Research, which enables investigators to acquire new research capabilities in the use of human or animal embryonic, adult, or cord blood stem cells, and the Mentored Quantitative Research Career Development Award, which encourages investigators from quantitative science and engineering fields to focus on questions of health and disease.

Coordination and Oversight by the NIH Office of Extramural Research

Much as NIH collaborates with grantee institutions in conducting research training, OER partners with ICs to coordinate and monitor awards for research training and career development across NIH. With active input from the ICs, OER establishes and implements policies and guidelines for each of the programs; determines broad national needs for basic biomedical, behavioral, and clinical research personnel; coordinates NIH-wide evaluations; develops trans-NIH research initiatives in which NIH ICs participate; and develops and maintains information systems to enhance program efficiencies. OER convenes monthly meetings of the NIH Training Advisory Committee to provide an agency-wide forum to identify and discuss issues related to research training and to provide opportunities to coordinate activities pertinent to the review, administration, management, and evaluation of training grants and fellowships.

Intramural Activities

The NIH intramural program provides opportunities for students, postdoctoral scholars, and clinicians to gain research experience within the more than 1,140 intramural laboratories of NIH[25]. A multifaceted array of programs provides a vibrant, scholarly environment and ensures strong research training experiences for future investigators and the continued professional development of intramural scientists.

Summer internships are available for high school, college, and graduate students. Recent college graduates who plan to apply to graduate or professional school can spend a year engaged in biomedical research working side by side with NIH scientists. Current graduate students can spend a summer, or even a year, as fellows engaged in biomedical research at NIH. The Graduate Partnerships Program (GPP) enables students to pursue research at NIH toward their degrees in partnership with a participating academic institution. By linking academic environments with the breadth and depth of research at NIH, the GPP creates a valuable graduate experience, one that purposefully focuses on skills of the future scientist and how discoveries will be made in the decades ahead. The Clinical Research Training Program (CRTP) is a yearlong program designed to attract the most creative, research-oriented medical and dental students to the NIH campus. CRTP fellows spend a year engaged in a mentored clinical or translational research project, in an area that matches their personal interests and goals.

[25] For more information, see http://www.training.nih.gov/

Training opportunities continue when scholars gain their graduate degrees. Year-round, NIH intramural laboratories employ fellows from the United States and abroad, creating a thriving, multidisciplinary intramural research community. The Postdoctoral Intramural Research Training Award provides the opportunity for recent doctoral degree recipients, who are U.S. citizens or permanent residents, to enhance their research skills in the NIH intramural environment. Trainees pursue both basic and clinical research. A parallel program, Visiting Fellowships, serves foreign national doctoral-level scientists. For clinicians, there are opportunities for residency and subspecialty training, including graduate medical education-accredited programs (for program completion data, see Appendix D). A wide array of accredited joint, NIH, and other sponsored programs are available. These GME programs enable research-oriented clinicians to weave research experience and training into their post-medical school training.

The intramural program also offers numerous targeted training programs and fellowships as varied as the Imaging Sciences Training Program, the NIH Dietetic Internship, and the Social Work Field Instruction Program. Many specialized programs address the need for a diverse research workforce, including the Women's Health Postdoctoral Fellowship, (Also see the *Minority Health and Health Disparities* section of Chapter 2).

All members of the NIH community benefit from access to a plethora of NIH courses, seminars, and science career resources. For example, every day across the NIH campus there are scientific seminars and frequent colloquia addressing the latest developments and discoveries in biomedical science; meetings of more than 100 Scientific Interest Groups that host forums and lecture series on cutting-edge issues of interest ranging from the Bioethics Interest Group to the Integrative Neural Immune Interest Group; and short– and long-term course offerings such as *"Introduction to the Principles and Practice of Clinical Research"* and *"Principles of Clinical Pharmacology."*

NIH Loan Repayment Programs

The NIH Loan Repayment Programs (LRP) are a vital component of our Nation's efforts to attract eligible doctoral-level professionals to research careers in fields of special importance—clinical, pediatric, health disparities, contraception and infertility, and AIDS research. To encourage qualified scientists to pursue research in these critical areas, the LRP provides financial assistance for educational debt in exchange for a 2- or 3-year research commitment. Program participants may receive up to $35,000 annually in loan repayment and can fulfill their commitments by conducting research in the specified fields in any nonprofit, university, or government organization, or as an NIH employee. The LRP serves the extramural and intramural communities by awarding LRP benefits to more than 1,600 research scientists annually[26]. Each program is competitive and serves to recruit talented biomedical scientists and physicians to research careers addressing important public health needs.

Conclusion

The initiatives and program reviews highlighted in the next section all point to the considerable progress made by NIH in meeting the long-term goal of building and maintaining research capacity to help ensure that highly trained scientists are available to address biomedical, behavioral, and clinical research needs, with the ultimate goal of uncovering new knowledge that will lead to better health for all Americans.

Notable Examples of NIH Activity

Key for Bulleted Items:
E = Supported through **E**xtramural research

[26] http://www.lrp.nih.gov/brochure.pdf

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 tracked under the **G**overnment **P**erformance and **R**esults **A**ct

Trans-NIH Initiatives and Major Programs

Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants (T32): The objective of the NRSA program is to support graduate and postdoctoral research training to help ensure that a diverse and highly trained workforce is available to carry out and lead the Nation's biomedical, behavioral, and clinical research agenda. This program supports predoctoral and postdoctoral research training programs at domestic institutions of higher education. The NRSA program has been the primary means of supporting graduate and postdoctoral research training programs since enactment of the NRSA legislation in 1974. Training activities can be in basic biomedical or clinical sciences, in behavioral and social sciences, in health services research, or in any other discipline relevant to the NIH mission. Institutional research training grants allow universities, research institutes, and teaching hospitals to select specific trainees and develop a curriculum of study and research experiences tailored to provide high-quality research training. The training grant award provides stipends and offsets the cost of tuition for appointed trainees.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-06-468.html
- For more information, see http://grants.nih.gov/training/nrsa.htm
- (E) (OD/OER)

Interdisciplinary Research Training Programs: The NIH Roadmap Interdisciplinary Research Teams of the Future program addresses the challenges of developing, sustaining, and administering interdisciplinary research and team science. Interdisciplinary research is the melding of multiple disciplines to arrive at new experimental approaches, and it requires the participants to be educated in more than one discipline. Although this is often accomplished through teams of investigators learning from each other via collaborations, formal training in multiple disciplines can allow individual investigators to develop interdisciplinary approaches. The NIH Roadmap Interdisciplinary Training Program consists of four initiatives that were intended to provide this type of formal training to investigators at all levels of their careers.

- *Training for a New Interdisciplinary Research Workforce*. These institutional training grants aim to catalyze the production of a scientific workforce capable of integrative research crossing traditional disciplinary boundaries. Awardees develop and implement novel training programs focused on interdisciplinary science.
- *Interdisciplinary Health Research Training*—Behavior, Environment, and Biology. Institutional Training Grants provide doctoral-level trainees with additional postdoctoral training in a new discipline. Trainees must either have been trained in the social and behavioral sciences or be seeking training in these areas. The intent is to encourage interdisciplinary approaches to complex health problems involving behavioral and social factors.
- *Short Programs for Interdisciplinary Research Training*. These programs range from 2 to 8 weeks in duration and are intended to provide an opportunity for investigators at all career stages to receive basic instruction in a new discipline.
- *Curriculum Development Award in Interdisciplinary Research*. These awards provide funds to develop creative curricula for interdisciplinary training. Once developed, these curricula are intended to be broadly available for use in multiple settings.

- For more information, see http://nihroadmap.nih.gov/interdisciplinary/fundedresearch.asp
- (E) (Roadmap—all ICs participate)

Training Activities of the Clinical and Translational Science Award Program: Comparing new disease treatments

and prevention strategies against those in current use requires dedicated clinical and translational research teams that include physicians, basic scientists, and statisticians and informatics experts, among others. Clinical research requires unique skills in addition to those needed to care for patients, so academic health centers must equip promising individuals with the special training they need to succeed in research careers. To address this need, NIH has expanded its clinical research training programs, first through the Roadmap T32 and K12 programs and, more recently, through Clinical and Translational Science Awards (CTSAs). Each program is based on placing the trainees in a mentored environment, where they learn the skills needed to cultivate multidisciplinary research team collaborations and design research projects to successfully compete for funding. The CTSA program will grow through 2012 to serve about 60 academic sites, providing research training and career development opportunities to a combined total of more than 1,200 trainees and new investigators covering multiple individual disciplines.

As mandated in Section 106 of the National Institutes of Health Reform Act (Pub. L. No. 109-482), NIH will conduct an evaluation and comparison of the outcomes and effectiveness of the CTSA training programs. This evaluation will be part of a much larger comprehensive evaluation of the CTSA program as a whole. Each individual CTSA is expected to include its training activities in its own evaluation. To coordinate and share information, including results of training activity evaluations, there is a CTSA Education/Career Development Steering Committee which provides a forum for the advancement of integrated and interdisciplinary education, training, and career development in the clinical and translational sciences and serves as a clearinghouse for clinical research training. Since the CTSA program was only recently initiated (September 2006), significant evidence of the long-term impact of the CTSA program is more likely to be measurable after 7 or more years. However, short-term process milestones and intermediate outcomes are expected in 1 to 7 years.

- For more information, see nihroadmap.nih.gov/clinicalresearch/overview-training.asp
- For more information, see http://www.ctsaweb.org/
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (Roadmap—all ICs participate)

The NIH Blueprint for Neuroscience Research: The Blueprint is a collaborative framework that brings together 16 NIH Institutes, Centers (IC), 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 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (**NINDS**, NCCAM, NCRR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, OBSSR)

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 2: *Infectious Diseases and Biodefense.*
- (E) (FIC, NCI, NHLBI, NIDA, NIDCR, NIMH, NINDS, NINR, OAR, ORWH)

Research Career Development Programs: One of the most challenging transitions in any research career is the transition from postdoctoral trainee to independent scientist. NIH has long used the Research Scientist Development Award (K01) to support the successful transition of individuals who hold a research or health-professional doctoral degree or equivalent, as well as newly independent investigators and midcareer investigators who need protected time to make a shift in their research careers or enhance their ability to conduct scientifically sophisticated studies in their chosen fields. Junior-level clinically-trained individuals are encouraged to apply for the Mentored Clinical Scientist Development Award (K08), or the Mentored Patient-Oriented Research Career Development Award (K23), as appropriate, to realize their potential to develop into productive clinical investigators. Transition awards such as the Career Transition Award (K22) and the Pathway to Independence Program (K99/R00) provide mentoring, protected time, and financial support to postdoctoral fellows seeking to transition to faculty positions. Many specific career development awards are tailored to meet the needs of different research areas and recipients at different career levels.

- For more information, see http://grants.nih.gov/training/careerdevelopmentawards.htm
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-06-001.html (K01)
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-06-512.html (K08)
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-05-143.html (K23)
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-06-133.html (K99/R00)
- (E) (OD/OER)

NIH Basic and Clinical Intramural Research Training: Candidates selected for NIH intramural research training and career development programs may be funded by any one of a number of mechanisms depending on availability of funding, the type of research to be conducted, the center or laboratory sponsoring the research, and qualifications of the candidate. These mechanisms include the NIH Postdoctoral Intramural Research Training Award (IRTA), which enables recent doctoral degree recipients to enhance their research skills by pursuing basic or clinical research at NIH, and the Clinical Research Training Program (CRTP), which enables research-oriented medical and dental students to engage in mentored clinical or translational research projects, again, in NIH laboratories.

- For more information, see http://www.training.nih.gov/postdoctoral/pdopps.asp
- (I) (OIR)

LRP Outreach Campaign: The NIH's Loan Repayment Program (LRP) “Strength in Numbers” campaign debuted September 6, 2007. This campaign offers a renewed commitment to qualified postdoctoral scientists who are seeking careers in biomedical and behavioral research. The program funds up to $35,000 annually in loan repayment for eligible individuals. From September 1 to December 1, 2007, the NIH accepted applications for health professionals pursuing careers in one of the five LRPs offered by the NIH (Clinical Research, Clinical Research for Individuals from Disadvantaged Backgrounds, Contraception and Infertility Research, Health Disparities Research, and Pediatric Research). The programs also provide reimbursement for Federal and State tax liabilities resulting from the loan repayment award.

- For more information, see http://www.lrp.nih.gov/HomePage.aspx
- (E) (OER)

Re-entry Program: The Re-entry Program, now supported by 23 NIH institutes, was originally developed to help fully trained scientists (women and men) reestablish careers in biomedical or behavioral science after taking time off to care for children or parents, or to attend to other family responsibilities. The program was expanded in concept and participants during FY 2006 and FY 2007 and provides administrative supplements to existing NIH research grants to support full?time or part?time research by these individuals in a program geared to update research skills and knowledge.

- For more information, see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-068.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-04-126.html
- (E) (**ORWH**, NIA, NIAAA, NIAID, NIAMS, NIBIB, NCI, NICHD, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NEI. NIGMS, NHLBI, NHGRI, NIMH, NINDS, NLM, NINR, NCRR, NCCAM, FIC, ODS)

NIH Working Group on Women in Biomedical Careers: Led by the NIH Director and the Director, ORWH, this working group is reviewing NIH policies and programs to determine ways to enhance the careers of women in science, research, and engineering. The working group is also reviewing recommendations from the National Academies Report: *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering* and concerns of intramural women scientists.

- For more information, see http://womeninscience.nih.gov/
- For more information, see http://www.nap.edu/catalog.php?record_id=11741
- (E, I) (**ORWH**, OD)

ORWH/Office of Intramural Training and Education Programs: NIH supports a series of training programs for postdoctoral fellows, graduate students, summer students, and postbaccalaureate trainees, as well as career enhancement workshops for intramural scientists.

- For more information, see http://www.training.nih.gov/postdoctoral/womenshealth.asp
- (I) (**ORWH**, OIR)

Intramural Program on Research on Women's Health (IPRWH): The IPRWH is a trans-NIH interdisciplinary collaboration on women's health and sex/gender research. The IPRWH consists of:

- The Women's Health Special Interest Group (WHSIG), which is a focused research interest group that, among other activities, sponsors scientific lectures of interest to intramural women's health researchers.
- The ORWH Women's Health Seminar Series, which features nationally recognized leaders in women's health research who present the latest information on topics important to women's health for the NIH extramural and intramural scientific and public communities.
- The NIH Women's Health Fellowships in Intramural Women's Health Research, which, in 2006, announced the selection of the first recipients.

- For more information, see http://orwh.od.nih.gov/news/iprwh.html
- For more information, see http://orwh.od.nih.gov/news/whsig.html
- For more information, see http://tango01.cit.nih.gov/sig/home.taf?_function=main&SIGInfo_SIGID=122
- For more information, see http://orwh.od.nih.gov/news/whss.html
- For more information, see http://orwh.od.nih.gov/news/2006Fellows.html
- (I) (ORWH)

IC-Specific Programs and Initiatives

Medical Scientist Training Program: The need for investigators who are well trained in both basic science and clinical medicine has long been recognized within the biomedical science community. To help meet this need, NIH established the Medical Scientist Training Program (MSTP). This program encourages and supports the training of

students with outstanding credentials and potential who are motivated to undertake careers in biomedical research and academic medicine. MSTP students participate in an integrated program of graduate training in the biomedical sciences and clinical training offered through medical schools. Graduates receive the combined M.D.-Ph.D. degree, and the majority of them pursue careers in basic biomedical or clinical research. MSTP grants are a type of National Research Service Award.

- For more information, see http://www.nigms.nih.gov/Training/InstPredoc/PredocOverview-MSTP.htm
- (E) (NIGMS)

NIGMS Community for Advanced Graduate Training (CAGT): To increase interactions between the Institute's MARC prebaccalaureate research training programs and its predoctoral graduate-level research training programs, NIGMS has created the Community for Advanced Graduate Training (CAGT) network. Launched in summer 2007, the CAGT is an interactive Web-based system that works to identify mentoring opportunities between MARC undergraduate students and NIGMS predoctoral research training grant program directors. The system aims to improve the ability of MARC students to find suitable predoctoral training opportunities and to apply directly to those graduate institutions. The system also will boost the ability of NIGMS research training grant program directors to recruit suitable students for their graduate (Ph.D.) programs. Moreover, MARC students will be able to access information regarding summer recruitment opportunities at these research-intensive graduate institutions.

- (E) (NIGMS)

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 International Clinical, Operational and Health Services Research and Training Award for HIV/AIDS and TB (ICOHRTA AIDS/TB) Program 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 who 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 2: *Infectious Diseases and Biodefense.*
- (E) (**FIC**, NCI, NHLBI, NIDA, NIDCR, NIMH, NINDS, NINR, OAR, ORWH)

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 infectious disease research expertise. This program supports U.S. and developing country institutions to train scientists from developing countries to engage in non-HIV/AIDS infectious disease research. It is contributing to the long-term goal of building sustainable research capacity in endemic infectious diseases at developing country institutions 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 2: *Infectious Diseases and Biodefense.*
- (E) (**FIC**, NIAID)

Informatics Training for Global Health: Information technology is required in almost all research programs, both to access the vast information resources available internationally and to apply to research design and analysis. This program is intended to increase the capacity of developing country scientists and medical professionals to design, access, and use modern information technology in support of health sciences research. Specifically, this program supports innovative training programs for developing country biomedical and behavioral scientists and engineers, clinicians, librarians, and other health professionals to increase their capacity to access, manage, analyze, interpret, manipulate, model, display, and share biomedical information electronically. Among other skills, this will increase their ability to conduct multisite clinical trials and international disease surveillance and prevention programs.

- For more information, see http://www.fic.nih.gov/programs/training_grants/itgh/index.htm
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems.*
- (E) (**FIC**, NHGRI, NIBIB, NLM)

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, Pan American Health Organization, and Centers for Disease Control and Prevention.

- For more information, see http://www.fic.nih.gov/programs/training_grants/trauma/index.htm
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (**FIC**, NHLBI, NIAAA, NIBIB, NIMH, NINR, OBSSR, ORWH)

International Training and Research in Environmental and Occupational Health: This program is building global capacity and collaboration to better understand, investigate, control, and prevent environmental and occupational health problems in developing countries and in the United States. Through this program, NIH is developing and strengthening centers of research excellence in environmental and occupational health-related sciences in target countries through long-term partnerships with U.S. institutions, with particular emphasis on research activities that will have the potential to benefit a whole region. The program was recompeted in 2007 and is jointly funded by NIH and the Centers for Disease Control and Prevention.

- For more information, see http://www.fic.nih.gov/programs/training_grants/itreoh/index.htm
- (E) (**FIC**, NIEHS)

International Training and Research Program in Population and Health: This program supports U.S. universities that provide training to scientists from developing countries in population studies or reproductive biology. Objectives of this program include enhancing population research programs and international collaborative studies on (a) reproductive processes and contraceptive development and (b) demographic processes, including aging, mortality, morbidity, fertility, migration, and linkages between health and economic development; strengthening the ability of scientists from developing nations to contribute to global population research efforts and advance knowledge in support of population policies appropriate for their home countries; and developing and strengthening centers of research excellence in population-related sciences in developing countries.

- For more information, see http://www.fic.nih.gov/programs/training_grants/itrph/index.htm
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (**FIC**, NICHD, ODS)

Interdisciplinary Training in Environmental Health Science and Genetics: The new Human Genes and the

Environment Training Program, as a part of the Genes, Environment and Health Initiative, will provide grants to train scientists in the emerging inter-discipline of environmental genomics/genetics to pursue a career path that integrates environmental sciences with human genetics and population genetics and genomics. This cadre of scientists will not only be equipped to advance methodologies and technologies in environmental genomics/genetics, but will also use these tools and resources to disentangle and evaluate the enormous number of environmental factors which directly influence or interact with some genotypes to determine the resultant phenotypic expression and clinical or physiologic endpoints associated with the etiology and treatment of complex diseases.

- For more information, see http://www.gei.nih.gov/traininggrants.asp
- (E) (**NIEHS**, NHGRI)

Predoctoral Research Training in Biostatistics: A workforce of biostatisticians with a deep understanding of statistical theory and new methodologies is vital to meet the biomedical, clinical, and behavioral research needs of the United States. With that end in mind, NIGMS has funded 13 predoctoral training programs in biostatistics to support 43 predoctoral trainees. The program was initiated at the request of several NIH institutes, which provided cofunding to help launch the effort. The training program integrates biostatistical theory and evolving methodologies with basic biomedical research, including bioinformatics, genetics, molecular biology, cellular processes, and physiology, as well as epidemiological, clinical, and behavioral studies.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/par-04-132.html
- (E) (NIGMS)

Predoctoral Training at the Interface of the Behavioral and Biomedical Sciences: In 2006, NIGMS announced a new institutional training grant program focused on "Training at the Interface of the Behavioral and Biomedical Sciences." The first two awards were made in July 2007. The programs provide an interdisciplinary research training experience and curriculum for predoctoral trainees that integrate both behavioral and biomedical perspectives, approaches, and methodologies. Through coursework, laboratory rotations, and programmatic activities that reinforce training at this interface, the program aims to develop basic behavioral scientists with rigorous training in the biomedical sciences who are available to assume leadership roles related to the Nation's biomedical, behavioral, and clinical research needs. This new training grant program is one of eleven predoctoral research training areas supported by NIGMS that promotes interdisciplinary, collaborative, and innovative research training.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-06-503.html
- For more information, see http://www.nigms.nih.gov/News/Results/BehavioralBiomedical070207.htm
- (E) (NIGMS)

Research on Interventions That Promote Research Careers: This new initiative funds research that will inform programs designed to increase the number of underrepresented minority students entering careers in mainstream biomedical and behavioral research. Comparative research will analyze the experience of all ethnicities in order to place that of underrepresented students in context and to learn whether and how interventions should be tailored to make more underrepresented students successful in biomedical careers. The results of this initiative could inform the NRSA training communities about diversity recruitment.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-08-005.html
- (E) (NIGMS)

NINR Intramural Training Initiatives: NIH concluded its 6th and 7th annual Summer Genetics Institutes (SGI) in June/July 2006 and 2007, respectively. The SGI is an intense, 2-month, full-time summer research training program targeted at faculty, graduate students, and advanced-practice nurses. Hosted by NINR's Division of Intramural

Research, the SGI features classroom and laboratory components that are designed to provide a foundation in molecular genetics for use in clinical practice and the research laboratory. The SGI develops research capacity among graduate students and faculty in nursing and provides a basis for clinical practice in genetics among advanced-practice nurses.

For recently graduated, doctorally prepared nurse scientists, NIH sponsors the K22 Career Transition Awards, which are designed to facilitate the successful transition of postdoctoral trainees to independent research careers. Awardees receive up to 3 years of postdoctoral research training in the NINR intramural laboratories in Bethesda, Maryland, followed by 2 years of extramural support as they begin tenure-track faculty positions. In addition, NINR participates in the NIH Graduate Partnership Program, in which the Institute partners with schools of nursing to support the research training of doctoral students in symptom management, genetics, or end-of-life/palliative care in the NIH intramural laboratories. In supporting such initiatives, NIH seeks to expedite the development of productive nurse scientists, many of whom can also go on to serve as nursing faculty.

- For more information, see http://www.ninr.nih.gov/Training/TrainingOpportunitiesIntramural/
- (I) (NINR)

Building Interdisciplinary Research Careers in Women's Health (BIRCWH): BIRCWH is an innovative career development program to support the training of junior faculty researchers in an interdisciplinary mentored environment in women's health research by pairing junior researchers with senior investigators. The program bridges advanced training with research independence, in addition to integrating scientific disciplines in an interdisciplinary nature. In FY 2006 and FY 2007, the BIRCWH program funded 36 additional awards.

- For more information, see http://orwh.od.nih.gov/interdisciplinary/bircwhmenu.html
- (E) (**ORWH**, ODS, NICHD, NIA, NIDA, AHRQ)

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 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (**ORWH**, NICHD)

Informatics Research Training Programs: To address the national need for computational scientists competent in biology and medicine, NLM reviewed its University Informatics Research Training Programs and issued a new call for applications. Curricula were updated to reflect current computing needs in clinical translational research and public health. Eighteen 5-year grants, totaling more than $75 million, for research training in biomedical informatics, were awarded in 2006. Approximately 270 trainees are currently enrolled in these programs.

- For more information, see http://www.nlm.nih.gov/ep/AwardsTrainInstitute.html
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems.*
- (E) (NLM)

Addressing the Unique Training Needs of CAM Research: NCCAM supports two unique NRSA funding opportunities for predoctoral and postdoctoral fellows who wish to be trained specifically in research related to complementary and alternative medicine. These programs support conventional researchers and trainees as well as CAM practitioners. NCCAM also supports NRSA institutional training grants (T32) through the NIH-wide mechanism. Many of the training programs supported are unique in that they accept CAM practitioners who wish to transition to a research career. Others involve collaboration between a conventional research intensive institution and a school that trains CAM practitioners. For example a partnership between Bastyr University School

of Naturopathic Medicine and the University of Washington provides postdoctoral training opportunities for CAM practitioners as well as individuals with conventional scientific academic backgrounds.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-384.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-07-319.html
- For more information, see http://grants2.nih.gov/grants/guide/pa-files/PA-06-468.html
- (E) (NCCAM)

International Research Scientist Development Award (IRSDA): Through IRSDA, Fogarty International Center 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, Fogarty 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 virus occurred between primates and bushmeat hunters. Dr. Wolfe has now received the NIH Director's Pioneer Award. Cofunded by Fogarty 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 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 2: *Infectious Diseases and Biodefense.*
- (E) (FIC, NIAID)

Public-Private Partnerships

Partnerships to Support Training for Research on Aging: NIH collaborates with private organizations and foundations to prepare scholars for research on aging. For example, partnerships with the American Federation for Aging Research, the John A. Hartford Foundation, and other foundation partners support two efforts:

- The Summer Research Training in Aging for Medical Students program provides a series of coordinated Institutional National Research Service Award (NRSA) grants designed to expose medical students, early in their training, to the excitement of ongoing research and encourage them to consider careers in research on aging.
- The Paul B. Beeson Career Development Awards in Aging Research offer 3- to 5-year faculty development awards to outstanding junior and mid-career faculty committed to academic careers in aging-related research, training, and practice. For over a decade, these awards have been extraordinarily successful in preparing participants to take leadership roles in research that has added exponentially to our understanding of aging and age-related diseases and conditions.
- A third partnership is with the Alzheimer's Association to support the unique and highly successful Summer Institute on Aging Research. For 21 years, this program has assisted emerging scholars in making the transition to independent funding for research relevant to aging. The program provides junior investigators an opportunity to be mentored in the substance and methodology of aging research by recognized experts in the field with the goal to enhance participants' potential for success as independent investigators. In 2004, the John A. Hartford Foundation partnered with NIH to sponsor a preconference to the Summer Institute to address issues of clinical research.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-05-002.html

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-07-001.html
- For more information, see http://www.nia.nih.gov/NewsandEvents/summer2007.htm
- (E) (**NIA**, ODS)

Research Training Partnerships: NIH has signed a Memorandum of Understanding with both the American Skin Association and the Orthopaedic Research and Education Foundation to provide supplemental support to fellows funded under the National Research Service Award program.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-06-536.html
- For more information, see http://grants.nih.gov/grants/guide/pa-files/PAR-06-539.html
- (E) (NIAMS)

HHMI-NIH Interfaces Initiative: Interdisciplinary research that builds from the foundations of multiple traditional disciplines including biology, physics, engineering, chemistry, informatics, and medicine has become an essential feature of modern biomedical research. Training the interdisciplinary researchers of the future and reducing the barriers to interdisciplinary graduate education is the goal of a public-private partnership between NIH and the Howard Hughes Medical Institute (HHMI). This initiative is developing cross-department mentoring programs, interdisciplinary courses, and a cadre of students being trained in an interdisciplinary environment. Programs are under development at 10 universities at the present time.

- For more information, see http://www.hhmi.org/grants/institutions/nibib.html
- For more information, see http://grants.nih.gov/grants/guide/notice-files/NOT-EB-05-002.html
- For more information, see http://www.nibib.nih.gov/Training/Predoctoral#HHMI
- (E) (NIBIB)

NIH Training Program Evaluation

Annual Assessments of Research Training: Every year, NIH assesses NRSA research training outcomes and program management against two goals established under the Government Performance and Results Act (GPRA). In the first of these goals, NIH seeks to measure the quality of its programs and ensure that substantial numbers of trainees and fellows are retained in research careers, by comparing the subsequent research activity of former NRSA trainees and fellows against their peers. The second of these two GPRA goal measures NIH progress on improving the efficiency of the NRSA program by developing and implementing an electronic system for appointing trainees to institutional training grants. By 2012, NIH expects the new system to be fully implemented and that 100 percent of trainees will be appointed to training grants electronically rather than through paper appointment forms. This is a new goal and NIH will report its performance in transitioning to electronic appointments in February 2009.

- For more information, see http://officeofbudget.od.nih.gov/PDF/FY08%20PB%20Performance%20Detail%20Vol%20II%20FINAL%20(PB%20Submitted).pdf
- (O) (OD/OER) (GPRA Goal)

Program Assessment Rating Tool (PART) Review of NIH Research Training: In 2006, NIH training programs underwent PART review by the Office of Management and Budget and received the highest rating possible. The OMB judged the NIH program to be "effective at training and retaining researchers in the biomedical research field," to be successfully meeting "its ambitious long-term and annual goals," and to have conducted independent evaluations of the program since its inception in 1974. The NIH training program also has a plan to improve performance and management over time, and held accountable for meeting improvement targets.

- For more information, see http://www.whitehouse.gov/omb/expectmore/summary/10003543.2006.html
- (O) (OD/OER)

Evaluation of Extramural Research Training and Career Development Programs at NIAMS: The NIAMS is currently conducting an outcome evaluation designed to examine the effectiveness of its research training (T32 and F32) programs and career development award (K01 and K08) programs.

- (O) (NIAMS)

Assessment of CAM Research Training Needs: A formal evaluation by an independent expert panel of opportunities for training in research on complementary and alternative medicine (CAM) highlighted the unique needs of the field. In particular, building capacity in the CAM research workforce requires specific efforts targeted at: 1) training CAM experts, who frequently have little scientific background, in scientific research methodology; and 2) creating opportunities for investigators from conventional scientific, who generally know little about CAM, to learn about CAM practices and modalities. This report continues to guide NCCAM's training initiatives which are aimed at creating programs to establish sustainable research training infrastructure, programs targeted to CAM practitioners, and career transition awards specifically aimed at helping CAM researchers establish independent research careers.

- For more information, see http://nccam.nih.gov/training/report.htm
- (O) (NCCAM)

Summary of Research Activities by Key Approach and Resource

Health Communication and Information Campaigns and Clearinghouses

When Ruth walked into the locker room at work, she realized something was wrong. She couldn't speak. She tried to pick up her lock, but her right hand couldn't grab it. Luckily, her friend knew the signs of stroke (sudden numbness or weakness of the face, arm, or leg–especially on one side of the body; sudden confusion; trouble speaking or understanding speech; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, or loss of balance or coordination; or sudden severe headache with no known cause) and called an ambulance. In the emergency room the doctors ran some tests and administered a clot-busting drug into her IV. Within 10 minutes she could speak again. Ruth didn't know a thing about stroke before she had one. Now, she makes sure that all the members of her family know the signs of stroke and that getting help within the first hour after a stroke, not waiting to see if it gets "better," is key to the best possible outcome–the outcome Ruth had.

After much investigation followed by clinical trials, scientists provided the treatment that enabled the good outcome for Ruth. But public knowledge, based on targeted and repeated dissemination of science-based information, using multiple avenues, helps the public reach the treatment. The Know Stroke. Know the Signs. Act in Time[27] *public education campaign helps build awareness of the symptoms of stroke and the need to act quickly.*

A listing of select NIH Education and Awareness Campaigns is online at:
http://www.nih.gov/icd/od/ocpl/resources/campaigns/

Introduction

Reaching the public in an efficient way with science-based, trustworthy information is an important part of NIH's mission. As the focal point of the national biomedical and behavioral research enterprise, NIH has a responsibility to communicate useful public health and science information to a wide range of audiences, including the public, patients, family members, health care providers, scientists, public health workers, voluntary health organizations, policy leaders, and industry. Strategic health communications and information campaigns and clearinghouses are the primary means NIH uses to fulfill this mission.

Health communication is a complex task. More than simply conveying information, it involves using carefully developed and tailored strategies and an armamentarium of appropriate tactics to inform individual and community decisions that contribute to enhanced health. Effective health communication requires:

- Needs assessment and preevaluation
- Environmental scans, that is, what is known and who are the interested parties
- Cultural competency
- Audience analysis

[27] For more information, see https://ice.iqsolutions.com/ninds/profstrokepubs.asp

- Defining core messages
- Finding audiences where they are
- Making the materials useful for each audience
- Careful selection of the appropriate channels of communication
- Constant reevaluation of the effectiveness of communications programs

To support the agency's health communications goals, NIH reaches out to the public through a variety of programmatic efforts. Public information campaigns are coordinated efforts to raise public awareness of critical health issues, and communications clearinghouses provide educational materials and resources on a variety of health-related topics. In addition to campaigns and clearinghouses, NIH also offers a wide variety of information resources utilizing the Internet, television, radio, print outlets, and other methods of communication. NIH Web sites are increasingly powerful communication tools, evidenced by the fact that they are accessed more than 1 billion times each year by health professionals, scientists, and the public. The role of intermediaries who use the Web, such as public health workers, demonstrates the additional powerful reach of clear, useful, accurate information produced by NIH, but delivered at the local level, tailored to the needs of the community or the individual.

Certain efforts may target specific audiences, such as populations that are at greater risk for particular diseases. Sometimes the communication effort is developed with the direct input of a community. Each communications approach has a different purpose, includes different elements, has the potential for reaching different audiences, and can be ongoing or time specific.

For example, an information campaign may be targeted to raise awareness or to take urgent and specific action based on a scientific discovery. This type of campaign must be carefully designed to reach affected audiences, which may include such diverse populations as patients, physicians, caregivers, industry, children, the aging, or, for example, women susceptible to heart attack or African American males susceptible to stroke, usually within a finite period of time. A campaign often consists of multiple communication products delivered via a variety of outlets and has the desired goal of either provoking a specific action or bringing about a behavioral change.

Clearinghouses are information development and dissemination services sponsored by NIH ICs. Some services provided by clearinghouses include working with the ICs to develop materials, evaluate programs, assist in responding to phone, mail, fax, and e-mail inquiries, and distribute free publications in hard copy and electronic formats.

Each year, NIH distributes nearly 30 million science-based, health information publications to requestors who rely on NIH and its news stories, press releases, and publications for authoritative information about the latest research developments while making more and more information available via the Web. Recent research has shown that a majority of Americans who request NIH information not only use it, but also share it with others. More than 40 percent who use Web materials related to health take that information with them to their physicians' offices.

Each IC shares a similar challenge: identifying and selecting appropriate communication outlets for key audiences. As a way to make knowledge more meaningful, NIH strives to present information in teachable moments and in culturally competent, accessible ways. These offices work directly with the intramural and extramural scientists in their mission areas to ensure that the materials they produce are based on the soundest science. The OD Office of Communications and Public Liaison (OCPL) provides leadership and guidance and speaks for NIH as a whole. The result of these efforts is a broad-based communication program that uses the best of both traditional and new approaches to reach vast, ever-emerging audiences.

Summary of NIH Activities

NIH ICs are congressionally mandated[28] to provide health information, based on scientific discovery, to the public. This is a significant component of NIH efforts to translate research to improve the health of the Nation. Health information resources also reflect the change in science itself. For example, scientific advances led to genetic testing, which makes it possible, in some cases, for an individual to know the likelihood of developing certain diseases. This in turn creates needs and opportunities for communication of preventive health information. The ability to intervene before the first sign of disease occurs, or to prevent disease through increased awareness, enables the public to be increasingly involved in monitoring their health and participating in their own care. Improving public knowledge about disease processes, opportunities for disease prevention, and treatment options helps raise the health literacy of the public in ways that improve the quality and length of life and reduce the burden of disease.

Advances in biomedical and behavioral research have brought our Nation's health care enterprise to the brink of a new paradigm, summarized by the "4 Ps" listed below.

- *Predictive*, the ability to determine an individual's risk for developing a disease
- *Personalized*, the ability to analyze each individual's health risks and individualize the treatment, dosage, or approach to disease
- *Preemptive,*, the possibility of preventing disease altogether
- *Participatory*, the importance of having the practitioner and patient work together as a team to develop a treatment plan.

While this new paradigm carries the possibility of keeping individuals healthier, it also means that people must become more involved in managing their own health and in making informed decisions. To meet this need, NIH is employing a wide variety of health communication approaches and making more information available through the most current range of communication outlets and strategies.

Technology now complements proven communication approaches, such as print materials. For some groups communication strategies that make use of technology may be more advantageous than traditional formats. With our changing population, it is important that materials are produced with culturally appropriate content and formats and delivered by the most effective and direct system available.

Delivering Health News to the Public

First and foremost, NIH is responsible for keeping the public informed about new developments in NIH research that affect health. In addition, putting a human face on a scientific finding not only helps the public understand research, but also helps them comprehend the practical implications of a research finding for their own health and behavior, critical information for public participation in improving health.

For individuals who may have questions about science and health research, NIH has developed general materials that can be used for answering basic questions. For example, a variety of vetted health information resources are available through NIH, including:

- A Web site with A-Z health information from all NIH Institutes and Centers
- "Research Results for the Public," a site that provides disease-by-disease descriptions of research progress and information to promote improved understanding of clinical research

[28] Although many ICs have specific language that is variable (some as specific as mandating clearinghouses or education programs or others indicating the responsibility to make science-based information available to the public), the general authority is covered by Section 402(e) of the PHS Act.

- "Get Involved at NIH," the gateway for public participation, input, and feedback
- "NIH & Clinical Research," a health information site that features podcasts, vodcasts, and radio programs in English and Spanish on clinical research
- "NLM Director's Comments," a prominently displayed link on the NLM Web site that features weekly podcasts by NLM's Director. These features are now available in Spanish in an effort to reach one of America's rapidly growing populations

Moreover, NIH continues to provide direct information to almost 900 radio stations each week. The NIH Radio News Service, more than 20 years old, is available to news and health programs nationwide and has been upgraded to improve access for those outlets. NIH programs also are broadcast to listeners on XM Satellite Radio through a radio feature called "NIH Health Matters." Also, NIH publishes *News in Health*, which is accessible monthly to public health workers, community centers, aging centers, voluntary health organizations, physicians, and hospitals.

The press, a major source of health information for the public, is an important transmission resource for NIH in ensuring that sound, research-based information is disseminated to the public. To help the press interpret medical information with greater ease and accuracy, NIH staff members work every day to provide background for media sources and identify key knowledgeable scientists to help reporters develop their stories. NIH also offers a free annual training course, "Medicine in the Media," now in its sixth year. The course offers opportunities for journalists to refine their ability to evaluate and report on medical research.

In addition, the NIH Office of Communications and Public Liaison, which is responsible for coordinating NIH communications efforts, has been building a network of public information officers at grantee institutions as a way to enhance knowledge exchange and the quality of information that reaches the public regionally.

However, the Web and related media are the new frontiers for delivery of NIH-based news to the public. NIH has intensified the evaluation of its Web sites. A redesigned NIH Web site, www.nih.gov, debuted this year and reflects new technologies, including customized streaming news feeds such as Really Simple Syndication (RSS) and podcasting and vodcasting, thereby bringing NIH research to the next generation of health consumers who rely on portable electronic devices for news. Every IC has the option of using this model in redesigning Institute sites. The NIH MedlinePlus Web site has extensive health information from all NIH components. By the end of FY 2007, MedlinePlus contained trusted information on more than 740 diseases and conditions, up from just 22 when it was launched in 1998. To improve consumers' understanding of medical concepts, MedlinePlus includes a medical encyclopedia and a medical dictionary, and extensive information on prescription and nonprescription drugs. It also provides links to directories of health care professionals and information about clinical trials (http://clinicaltrials.gov/). MedlinePlus was voted the top government news/information Web site in the American Customer Satisfaction Index during the second quarter of 2007. A spinoff, in the form of a new quarterly magazine, NIH MedlinePlus, brings the latest and most authoritative information on health conditions and diseases from NIH directly to patients in physicians' offices. *NIH MedlinePlus* magazine is distributed free of charge to 40,000 physician offices and can be downloaded online as well.

The agency also seeks to take advantage of available opportunities to bring news and information to the public on regional, local, and community levels. A new feature of the MedlinePlus Web site provides more than one-third of Americans with a "Go Local" capability that puts them in touch with health resources in their communities. Go Local has links to health care information and resources in 22 States and regions; 11 of the Go Local sites were added in 2006 and 2007 and several more are in development.

Reaching Different Audiences

The "public" is not monolithic. It includes a number of audiences divided by gender, age, race/ethnicity, susceptibility to specific diseases, and many other factors. There are patients, families, friends, scientists, health professionals, public health workers, industry, health care providers, congressional staff, and voluntary organizations, all requiring specialized information related to specific health conditions or concerns, such as aging,

diabetes, or cancer. NIH responds to the requirements of specific audiences in a variety of ways.

Understanding different audiences and how to reach them is key to all public health communications programs supported by NIH. NIH develops communications programs that take into account groups that need specialized information, such as Latinas with an increased risk for diabetes, or African American males who suffer disproportionately from prostate cancer. In other cases, for example, providing parents with information about early identification programs in autism, hearing loss,or delayed language development can help them to work with their physicians to identify interventions that improve the lives of their children before a window of opportunity is lost. There must be multiple approaches and repeated messages to reach multiple audiences: NIH continues to produce science-based factsheets, checklist resources, public service announcements, podcasts and vodcasts (video podcasts), as well as other information resources concerning timely issues such as heart disease, depression, drug abuse, and eye health, each tailored for a specific audience, such as African Americans, the aging population, or teens.

NHGRI and NIDA both have sponsored major online events to provide opportunities for students and teachers in classrooms across the United States to ask real-time questions of the Nation's top scientific experts in the fields of genomics and drug abuse and addiction. The most recent event, NIDA's Drug Facts Chat Day, drew 36,000 questions. This is a format that NIH will continue to pursue.

In March 2007, the Office of Research on Women's Health began podcasting " Pinn Point on Women's Health," hosted by its Director, Dr. Vivian W. Pinn. The monthly podcast discusses the latest news in women's health research.

NIH also recently launched the Clinical Research Awareness initiative. This effort originates in the cultural shift taking place in medical care, a move away from physician referral to self-referral to clinical trials. This shift has created a different need for the public interested in participating in clinical research. As a result, there is a need for clear, easy-to-access information. NIH, with the NIH Clinical Center, has designed a Web site that includes information about (1) the nature of clinical trials, (2) what participation means, and (3) current trials and their locations, all with the goal of increasing public awareness and participation (http://clinicalresearch.nih.gov).

NLM supports www.clinicaltrials.gov is a website, a database of clinical trials past and current. This is a congressionally mandated[29] database that is adding features to make it more user-friendly. Because of the demand for information on cancer, NCI has developed a series of materials specifically about cancer clinical trials. The NCI Web site offers a range of resources, including a guide for patients and their families; worksheets to engage the community in outreach efforts related to cancer clinical trials; online courses for health professionals; DVDs; and slide sets to assist in education programs (see https://cissecure.nci.nih.gov/ncipubs/). The goal of these efforts is to help the public–patients, families, medical professionals, and the media–gain access to information on clinical research and its benefits.

NCCAM is NIH's source of evidence-based information about complementary and alternative healing practices. Increasingly, people are investigating what alternative treatment options are available, especially for hard-to-manage conditions such as chronic back pain. A 2006 survey completed by AARP and NCCAM revealed that nearly two-thirds of adults older than age 50 are using complementary and alternative medicine, but only one-third of them are sharing that information with their physicians. Just as clinical trials are becoming an integral part of the public's knowledge base, so also is complementary and alternative medicine. To encourage an open dialogue, NCCAM launched a new patient/provider education initiative, "Time to Talk," which encourages open discussion of all health care practices to ensure safe and coordinated care.

"Time to Talk" is only one example of how NCCAM is realizing its mission of exploring complementary and

[29] The original mandate, the Food and Drug Modernization Act of 1997 (Pub. L. No. 105-115), was enhanced by the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85).

alternative medicine in the context of rigorous science and then disseminating this information to the public. NCCAM's Web site received more than 2.6 million visitors in 2006 and has been cited by Prevention magazine for "Best Alternative Medicine Information." In addition NCCAM has been cited by the World Health Organization as a model for evidence-based CAM.

The population is aging rapidly, and seniors are a special focus of NIH's information dissemination efforts. As the Internet becomes an increasingly important source of information on health, seniors unfamiliar with using computers are being invited to use this new resource. NIA and NLM have joined forces to develop and maintain www.NIHSeniorHealth.gov, a site with credible, aging-related health information targeted to the cognitive and visual equirements of older adults. The site covers such topics as Alzheimer's disease, cataracts, colorectal cancer, and diabetes in a clear, easy-to-read format. Twelve NIH Institutes collaborated with NLM to develop the 33 health topics included on the site.

Print materials specially targeted to the issues of interest to older adults remain a primary way to provide information to seniors. The National Institute on Aging Information Center (NIAIC) and the Alzheimer's Disease Education and Referral (ADEAR) Center send millions of publications to older adults each year. These cover the latest findings about Alzheimer's disease, advice on long-distance caregiving, materials about the importance of exercise, and tips for improving communication with health care providers. The popular Age Page series of factsheets presents varied information tailored to seniors and these publications can be read online or downloaded. The wealth of materials specifically targeted to seniors reflects NIH's recognition of the importance of reaching out to this expanding audience.

Ethnicity can also require targeted communication strategies. NIH recently updated its Spanish-language Web site (http://salud.nih.gov). One of the major additions to this Web site is the inclusion of Spanish-language radio programming (http://salud.nih.gov/radio.asp). The Spanish-language radio site does not mirror the English site, but features information of particular interest and importance to Spanish-speaking communities at higher risk for specific diseases.

Some NIH communications programs target a population vulnerable to or with a specific disease. For example, NINDS developed the Know Stroke. Know the Signs. Act in Time public education campaign to help build awareness of the symptoms of stroke and the need to act quickly. New treatments are available that greatly reduce the serious losses associated with stroke. Knowing stroke symptoms, calling 911 immediately, and getting to a hospital are all essential for preventing lifelong disability. This is a dramatic example of the need for the public to know what science has learned about prevention or treatment of disease.

The Heart Truth, the NIH national awareness campaign for women concerning heart disease includes locally sponsored events, dissemination of materials, and free health screenings. Additionally, the campaign reaches physicians to raise awareness of the sometimes overlooked vulnerability of women to heart disease.

The National Kidney Disease Education Program, an initiative that has elements of both a campaign and a clearinghouse, disseminates educational materials tailored to minority groups at high risk and encourages dialogue about kidney disease among African American families. NIH also reaches out to specialized populations, including Native Americans, Asian Americans, those living in Arctic regions, and the elderly, through multiple Web sites that have features designed to meet the unique needs of each group.

The audiences are not only national–NIH reaches out to international audiences through collaborative communication campaigns about global health and emerging diseases issues such as avian flu, SARS, and HIV/AIDS through Institutes such as NIAID and through FIC programs.

NIH has a special role serving the public with information about rare diseases. The NIH Office of Rare Diseases provides an informational database and a clearinghouse resource for answering questions about diseases often misunderstood and misdiagnosed.

Rapidly Responding to Time-Sensitive Issues

In developing its communication programs, NIH anticipates and responds to current needs. From recognizing the physical and mental health needs of Hurricane Katrina victims to becoming aware of the growing problem of substance abuse and addiction among young people, NIH continues to respond with appropriate communications materials. Increasingly, it is becoming evident that children and adolescents are in need of tailored information resources to help them cope with health conditions, peer pressure, and life events, such as the death of a sibling or parent from disease. To address this trend, NIMH developed a number of brochures designed for parents, community members, and rescue workers that explain how to help young people through crises. These materials are readily available on the NIMH Web site.

Since 2004, NIAAA has taken on the difficult challenge of underage drinking. NIAAA launched its Underage Drinking Research Initiative with the goal of obtaining a more complete and integrated scientific understanding of factors that promote initiation, maintenance, and acceleration of alcohol use among young people. The initiative also addresses variables that influence the progression to harmful use, abuse, and dependence. A unique aspect of this research is that it is framed within the context of overall psychological and neurological development. NIAAA's landmark initiative on underage drinking features Web sites tailored to teens and college students and other resources.

The initiative has already led to concrete changes. First, it provided the scientific foundation for the March 2007 Surgeon General's Call to Action to Prevent and Reduce Underage Drinking. It also is the basis for the ongoing work of the Interagency Coordinating Committee on Preventing Underage Drinking. In addition, a series of meetings focusing on diagnosing alcohol use and disorders among youth and screening for adolescent drinking have been held, and a supplement of seven developmentally focused papers covering a broad range of underage drinking topics has been accepted for publication in *Pediatrics*.

This year, NIDA and NIAAA partnered with Home Box Office (HBO) and the Robert Wood Johnson Foundation to produce the documentary *ADDICTION*, which aired in spring 2007 on HBO. The documentary's nine segments explore new thinking about addiction as a brain-based disease and the role imaging has played in enhancing our understanding of drug and alcohol use, thereby leading to new treatments. NIH-sponsored research also is playing a key role in removing the stigma that surrounds addiction, an important step in helping the 22.6 million Americans with this disease seek and obtain treatment. *ADDICTION* was honored with a Governors Award by the Academy of Television Arts and Sciences (an Emmy), the highest honor given by the Academy, reserved for individuals or organizations committed to important social causes. More than 13 million people saw the documentary when it aired in March 2007. Millions more have accessed the content through DVDs sold in bookstores and at HBO.com, podcasts, Web streams, a companion book, local and national outreach parties and screenings, and prominent local and national media coverage. Much of the outreach was coordinated by addiction and recovery advocacy groups, including Community Anti-Drug Coalitions of America, Join Together, and Faces and Voices of Recovery with support from the Robert Wood Johnson Foundation.

The airing of *ADDICTION* was accompanied by the release of two publications, NIAAA's *Helping Patients Who Drink Too Much* and NIDA's Drugs, Brains, and Behavior–*The Science of Addiction. Helping Patients Who Drink Too Much* is an update of a 2005 edition and is targeted to primary care and mental health clinicians. It includes revised screening tools and tips for managing patients with heavy drinking and alcohol use disorders. The updated edition also has new resources, including education credits for physicians and nurses (available through Medscape); support for medication-based therapy in nonspecialty settings; a new handout with strategies to help patients reduce or quit drinking; a new dedicated Web page devoted to the Guide; supporting resources for clinicians and patients; and an updated PowerPoint presentation for educators. The second publication explains in lay terms how science has revolutionized our understanding of addiction as a brain-based disease. It also identifies risk factors for developing an addiction, lists prevention strategies, and suggests new approaches to treatment.

Recognizing Problems and Taking Action

In recent years, physicians and researchers increasingly have become aware of the issue of literacy as it relates to

health. Researchers have found that almost one-half of the Nation's adults have trouble reading instructions or interpreting information from a graph or chart. As a result, many people do not understand the instructions they receive from their health care providers[30]. Researchers also have found that low health literacy is more common among older Americans and is linked to socioeconomic status; more than 66 percent of adults age 60 or older have marginal literacy skills, and 45 percent of all functionally illiterate adults live in poverty[31].

The HHS Healthy People 2010 initiative established improving health literacy by the end of the decade as a national health objective. The term "literacy" refers to the mastery of a range of abilities, including reading, comprehending, and analyzing information; decoding instructions, symbols, charts, and diagrams; weighing risks and benefits; and, ultimately, making decisions and taking action. For example, to be considered "health literate" an individual should be able to understand instructions given by physicians; instructions on medication labels; information in health publications and on informed-consent documents; and data outlined on medical and insurance forms. A significant precept of health literacy is the ability of the individual to understand and take action. Health literacy arises from a convergence of education, health services, and social and cultural factors, and brings together research and practice from diverse fields. This challenge has particular relevance for health communications professionals, who must consider health literacy when developing health materials and communications strategies for different audiences, each with differing abilities, experiences, levels of knowledge, and cultural beliefs and practices. By understanding these differences, professionals can develop appropriate materials that have a greater potential for improving health and preventing disease. Through health literacy efforts designed to help both the receivers and providers of health information, NIH can improve health outcomes.

NIH has both scientific and communication initiatives in place to address the formidable challenges of health literacy. OBSSR coordinates the trans-NIH initiative of scientific grants on health literacy that is building national capacity for research on this issue. Studies under way are examining the relationship between health literacy and patient adherence, strategies such as using medical interpreters for patients with limited English proficiency, and an electronic data entry tool to help parents of children with attention deficit hyperactivity disorder communicate with health care providers, regardless of literacy levels.

NIH's Office of Communications and Public Liaison (OCPL), connecting the research with the public and serving as liaison to HHS on health literacy activities, has established the "Clear Communication," initiative that is focusing on objectives of health literacy–providing information in the form and with the content that is accessible to specific audiences based on cultural competence and incorporating such tactics as plain language and new technologies. The first phase of the "Clear Communication" program involves building upon sound research results provided by the trans-NIH initiative. OCPL is creating a number of resources to help the trans-NIH communicators and health communicators outside NIH reach audiences "where they are" and overcome health literacy barriers. One program is redevelopment of the nationally recognized resource "Making Health Communication Programs Work" which comprehensively addresses clear communication and reflects the best practices of all NIH ICs as a shared resource. OCPL maintains a resource Web site that includes synopses of research work under way and will house research results as they become available.

Sometimes health issues span Institutes and can be coordinated through offices in the Office of the Director to bring attention to identified problems. For example, an estimated 14 million American women may have vulvodynia (chronic vulvar pain) at one point in their lives, although for many women the condition remains undiagnosed. Vulvodynia can have a profound impact on a woman's quality of life. The Office of Research on Women's Health (ORWH) is addressing the needs of women in understanding the disease and physicians in recognizing it.

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[30] Talking the Talk, Law of Averages: Casting a Wide Net in Health Literacy Efforts with Rima Rudd, Sc.D.; *Facts of Life: Issue Briefings for Health Reporters*, Vol. 8, No. 3, March 2003.

[31] Talking the Talk, 2003.

Health disparities for many minority populations are often further exacerbated by poor access to health information. Recognizing this problem, NIH has programs in place designed to advance the health of minorities. The National Network of Libraries of Medicine (NNLM), which has more than 5,800 full and affiliate members, is the core component of NLM's outreach programs. Partnering with community organizations, NNLM has funded many projects, such as the Consumer Health Resource Information Service, which is located in 21 churches across the State of Tennessee. The program aims to provide the congregations with health information twice a month. In addition, health screenings, such as blood pressure checks, also are made available. NNLM continues to grow with the addition of public libraries at the community level that are joining the health sciences libraries as network members.

The Early Detection of Oral Cancer campaign is another NIH program designed to eliminate health disparities. The program is centered on developing educational materials concerning oral cancer targeted toward African American men, who have the highest risk of oral cancer and the lowest 5-year survival rate–only 35.6 percent. The first piece is a brochure called *Are You at Risk for Oral Cancer? What African American Men Need to Know* and is being pretested in Washington, D.C.; Chicago; Los Angeles; and Columbia, South Carolina. The brochure is part of a series of educational tools, including factsheets, posters, and print and audio public service announcements that will be targeted for distribution to African American community groups across the country.

In addition to developing materials, NIH reaches out to minorities by developing communications networks, such as the American Indian and Alaska Native (AI/AN) Health Communications Workgroup, established by NIAMS in 2005 with other ICs. Comprising representatives from a number of NIH ICs, the workgroup has presented two seminars: "Taking Action: Health Promotion and Outreach with American Indians and Alaska Natives" and "Cultural Competency Strategies for Indigenous Health Promotion… A Dakota Perspective." In 2007, the workgroup finalized a literature review begun for the Taking Action seminar by experts, internal and external to NIH, and published the review to be widely distributed to the public, especially health communicators.

Eliminating health disparities is a continuing challenge requiring persistence. NICHD's Sudden Infant Death Syndrome (SIDS) Outreach in Minority Communities campaign is a case in point. The program is in its 13th year, and death rates from SIDS have declined by 50 percent among African Americans. Nonetheless, infants from this community are still twice as likely to die from SIDS as are White infants. NIH is collaborating with national African American women's organizations to support community and neighborhood workshops that focus on 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 nation, small stipends from NIH help community organizations conduct SIDS risk-reduction workshops in rural areas.

An innovative community-based program called *We Can*! (Ways to Enhance Children's Activity & Nutrition), begun in 14 communities nationwide, including Boston, Massachusetts, and Montgomery County, Maryland, is addressing the national childhood obesity epidemic by providing educational programs and materials. *We Can*! materials include tips on how to encourage healthy eating, increase physical activity, and decrease sedentary activity, or "screen" time, such as TV watching.

Partnering With Health and Advocacy Organizations

NIH ICs receive regular input from nonprofit groups, such as voluntary health agencies, and these organizations can increase the reach of NIH health communications and outreach programs. NIH interactions with health and advocacy organizations range from routine meetings to the establishment of novel programmatic initiatives and partnerships. Such programs allow for cofunding of research, nonprofit input into the design and scope of NIH research initiatives, and the creation of new programs and collaborations. These efforts also enable NIH to receive regular input from its public constituencies and to forward research announcements, research results, agency news, and scientific press releases. Just a few examples include:

- NCI created CARRA–Consumer Advocates in Research and Related Activities–to draw on the experience of people affected by cancer to represent the views of cancer survivors and family members with respect to

the agency's daily activities.

- NIMH sponsors an Outreach Partnership Program that enlists national and State organizations in partnerships to help bridge the gap between research and clinical practice by disseminating the latest scientific findings; nforming the public about mental disorders, alcoholism, and drug addiction; and reducing the stigma and discrimination associated with these illnesses.

- NIAMS is working with a coalition of professional and voluntary organizations, all concerned with the agency's programs and findings related to diseases of bone, joints, muscle, skin, and connective tissues.

- An NIH Partners in Research Program supports 2-year pilot and/or feasibility studies of innovative activities designed to improve public understanding of biomedical and behavioral research, develop strategies for promoting collaboration between scientists and the community to improve the health of the public, and identify the conditions (e.g., settings and approaches) that will enhance the effectiveness of such activities. The long-term objectives of this initiative are (1) to study methods and strategies to engage and inform the public regarding health science in order to improve public understanding of the methods and benefits of publicly funded research and (2) to increase scientists' understanding of and outreach to the public in their research efforts.

Outreach to the Scientific and Research Communities

In addition to communicating science and health news and information, NIH reaches out to the scientific and research communities to share information and obtain input on policy issues. For example, in 2006 when NIH undertook the update of its data-sharing policies for research applications involving genome-wide association studies, NIH initiated a public consultation process to inform NIH policy development. This included a town hall meeting and, later, a formal Request for Information on the proposed policy that was issued in the Federal Register and publicized via press release. Currently, NIH is engaged in a profound effort to enhance its peer review system. The effort was launched in summer 2007 with a listening, or consultation phase, to ensure that NIH's examination of the system is informed by the concerns and ideas of stakeholders. Widely publicized regional meetings with the biomedical research community, local meetings with professional societies and health advocacy groups, a Web page taking online comments, and Federal Register Request for Information were all part of the outreach.

In addition, in the last year and on a quarterly basis, the NIH Director has begun communicating directly to voluntary health agencies, the interested public, policy leaders, extramural grantees, administrators, and research program offices. These "From the Desk" communications have been effective in giving and soliciting information.

Conclusion

As the paradigm for health care in the 21st century continues to evolve, NIH strives to develop appropriate communication outlets for its varied audiences. With consumers more involved in health and health care decision-making, the need for authoritative and timely information, delivered through the right conduits in the right forms, is all the more compelling. NIH is refining and reshaping its rich and varied communications program, focusing on certain topics and targeting specific populations as appropriate. It is using all the new avenues of technology–the Web, narrowcasting of television and radio, and the full range of new media–to communicate key health messages in forms and formats that resonate with the needs of diverse audiences. NIH will continue to evaluate how it reaches its audiences, always searching for innovative ways to keep the public informed about the latest developments in science and medicine in order to improve health.

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

Delivering Health News and Information to the Public

Clinical Trials Education: Materials 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, visit http://cancer.gov/publications
- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Clinical and Translational Research.*
- (E/I) (NCI)

New Publications: In FY 2006, NIH distributed 3.1 million publications on mental disorders. During this year, NIH also released two new publications: *Anxiety Disorders and Schizophrenia*. In FY 2007, NIH developed a series of booklets and factsheets about what community members, parents, and rescue workers can do to help children cope after violence and disasters.

- For more information, see http://www.nimh.nih.gov/health/publications/schizophrenia/summary.shtml
- For more information, see http://www.nimh.nih.gov/health/publications/anxiety-disorders/nimhanxiety.pdf
- For more information, see see http://www.nimh.nih.gov/health/publications/index.shtml
- (E) (NIMH)

MedlinePlus/MedlinePlus en Español: NIH employed new methods to increase awareness of its MedlinePlus databases. Weekly podcasts by NLM's Director were initiated to provide timely reports on health news; *NIH MedlinePlus The Magazine* was rolled out at a press event on Capitol Hill attended by members of Congress and guest celebrity Mary Tyler Moore, featured on the cover. The magazine is distributed free to 40,000 physician offices and has covered stories on cancer, diabetes, and heart attack. NIH expanded the content and features of the English and Spanish MedlinePlus Web sites and the associated GoLocal sites that provide information on local health resources for approximately one-third of the U.S. population. MedlinePlus was one of two U.S. winners of the 2005 Award at the World Summit on the Information Society.

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

Toxicology and Environmental Health: To inform the general public about toxicology and environmental health, NIH developed several new tools, including ToxMystery®, an interactive learning site for 7- to 10-year-old children; and Tox Town®, which uses color, graphics, sounds, and animation to enhance learning about chemicals, the environment, and public health.

- Hochstein C, Szczur M. *Med Ref Serv Q* 2006 Fall;25:13-31, PMID: 16893844
- For more information, see http://thunder1.cudenver.edu/cye/abstract.pl?n=87
- For more information, see http://sis.nlm.nih.gov/enviro/especiallystudents.html
- (I) (NLM)

Medicine in the Media Course: NIH presents a free annual training opportunity to help develop journalists' ability to evaluate and report on medical research. Now in its sixth year, the course examines the challenges and opportunities inherent in the process of communicating the results of medical research to the public. Stressing an evidence-based approach and reexamining intuitive beliefs about medicine, the course prepares participants for the crucial task of interpreting and evaluating research findings including statistics, selecting stories that hold meaningful messages for the public, and placing them in the appropriate context. Sessions are interactive, with hands-on opportunities to apply lessons learned, and incorporate journalists' special perspectives on the public's need for useful medical knowledge. The "Medicine in the Media" program was created to address a growing need to improve the reporting of scientific and medical research findings by the media. The program is highly competitive and attracts media and journalism professionals from around the country for a 3-day intensive workshop. The interactive program lays out the critical basics of differentiating strong from weak scientific information, well-designed versus poorly designed scientific studies, and "strength of opinion versus the strength of evidence." Feedback from participants indicates that the program changed their fundamental understanding of scientific news in terms of what is worthy of reporting and providing appropriate context when covering new research findings and a balanced presentation of the strength and relevance of the findings. Participants frequently recommended the program to colleagues.

- For more information, see http://medmediacourse.nih.gov/
- For more information, see http://medmediacourse.nih.gov/html/MiMAgenda040907.pdf
- (E) (OMAR)

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 upon print and radio public service announcements and on printed informational materials intended for distribution to COPD patients, to persons at risk for the disease, to health care professionals, and to community-level 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 2: *Chronic Diseases and Organ Systems*
- (E) (NHLBI)

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. The 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 2: *Minority Health and Health Disparities*.
- (E) (**NIDDK**, CDC)

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 to 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 screen (such as television) 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 2: *Chronic Diseases and Organ Systems*.
- (E) (**NHLBI**, NCI, NICHD, NIDDK)

National Eye Health Education Program (NEHEP): This program focuses on public and professional education programs that encourage early detection and timely treatment of glaucoma and diabetic eye disease and the appropriate treatment for low vision. A formal planning process in 2006 outlined a 5-year agenda for NEHEP that will now include programs in age-related macular degeneration and meeting eye health needs of older adults. The travelling "EYE SITE" exhibit has toured the Nation, working with over 100 vision-related organizations to offer more than 250 public events since 2001. The NEHEP Partnership with public and private organizations coordinates development and dissemination of education programs targeted to a variety of audiences.

- For more information, see http://www.nei.nih.gov/nehep/pdf/NEHEP_5_year_agenda_2006.pdf
- (O) (NEI)

Alzheimer's Disease Education and Referral (ADEAR) Center: The ADEAR Center is the Federal government's primary source of information for patients, caregivers, health providers, policymakers, and the general public on Alzheimer's disease and age-related cognitive change, including diagnosis, treatment, services, and research. The Center maintains a national database of clinical trials and develops easy-to-read materials in English and some in Spanish.

- For more information, see http://www.nia.nih.gov/Alzheimers
- (O) (**NIA**)

NIA Information Center (NIAIC): Through its Web site and toll-free telephone lines, the NIAIC provides information, available in English and Spanish, aimed at maintaining and improving the health of older adults by encouraging them to exercise, providing advice on long-distance caregiving, suggesting ways to improve communication with health care providers, and providing the latest information about research on aging. *Age Page* factsheets offer comprehensive, easy-to-read information on nearly 50 topics. A new Web-based newsletter will provide updates on health and NIA activities to the public, policymakers, and researchers.

- For more information, see http://www.nia.nih.gov/HealthInformation/Publications/
- (O) (NIA)

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 (MSM), and women at high risk of HIV infection. The goal is to increase awareness of 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 2: *Infectious Diseases and Biodefense.*
- (E) (NIAID)

Information Clearinghouses: NIAMS operates the NIAMS Information Clearinghouse and the NIH Osteoporosis and Related Bone Diseases National Resource Center. These clearinghouses produce and distribute health education materials to patient and health professionals on a variety of diseases of bone, muscle, joint, and skin. The Resource Center also manages the health promotion plans associated with the recent Surgeon General's report on bone health and osteoporosis.

- For more information, see http://www.niams.nih.gov/Health_Info/default.asp
- For more information, see http://www.niams.nih.gov/bone/index.htm
- (O) (NIAMS)

NIDCD Information Clearinghouse: NIDCD's Information Clearinghouse disseminates free health information in the areas of hearing, balance, smell, taste, voice, speech, and language to inquiring members of the public. For the years 2006-2007, the NIDCD Information Clearinghouse has maintained a toll-free phone and TTY number for the public and has ensured that NIDCD publications remain current and timely by adding or updating bilingual factsheets and other educational materials for dissemination to the public. In addition, Clearinghouse staff attended or provided materials for exhibits at 31 professional conferences and health fairs around the country. Clearinghouse staff also performed research to help in the planning of the new noise-induced hearing loss campaign. This included conducting focus group testing and leading a workshop seeking input from key advocacy organizations.

- (O) (NIDCD)

WISE EARS!®: WISE EARS! is NIH's national public education campaign against noise-induced hearing loss (NIHL) to increase awareness among the public and workers. For the years 2006-2007, NIH distributed free bilingual WISE EARS! materials, available online and through its toll-free information clearinghouse, to health professionals, students and teachers, community organizations, government officials, and the general public. NIH also conducted an evaluation of the WISE EARS! program to determine how well the campaign is meeting its objectives and to make recommendations for the future direction of the campaign. Based on the evaluation's key findings, NIH now plans to refocus its NIHL campaign by targeting children ages 8 to 12, by forging more mutually beneficial partnerships, and by making use of delivery channels with the highest potential to attract and engage its audience.

- (O) (NIDCD)

Exhibitions for the Public: NIH continues to present lively and informative exhibitions that enhance the awareness and appreciation of science, medicine, and history. Changing the Face of Medicine: Celebrating America's Women Physicians closed in FY 2006 after a highly successful 25-month run, but lives on in a traveling version that is touring the country. A new exhibition, *Visible Proofs: Forensic Views of the Body*, opened in February 2006 and will continue until early 2008. Scores of school and community groups visit the exhibitions at NLM.

- For more information, see http://www.nlm.nih.gov/hmd/about/exhibition/index.html
- (I) (NLM)

Genetics Home Reference: The Genetics Home Reference Web site provides basic information about genetic conditions and the genes and chromosomes related to those conditions. Created for the general public, the site was expanded to include summaries for more than 225 genetic conditions, more than 380 genes, all the human chromosomes, and information about disorders caused by mutations in mitochondrial DNA.

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

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://cancer.gov/publications, 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 2: *Cancer*.
- (E/I) (NCI)

Reaching Different Audiences

Podcast on Women's Health: In 2007, NIH began a series of podcasts entitled "Pinn Point on Women's Health" featuring ORWH Director Dr. Vivian W. Pinn in conversation with other NIH scientists. The podcasts highlight extramural and intramural research and current topics of importance to sex/gender and women's health.

- For more information, see http://orwh.od.nih.gov/podcast/podcast_archive.html
- (E, I) (ORWH)

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 2: *Minority Health and Health Disparities*.
- (E/I) (**NIDCR**, NCI)

Evidence-Based Information on CAM:

- NCCAM provides extensive sources of evidence-based information on CAM through its Web site and clearinghouse. In 2006 its Web site had more than 2.6 million visitors and was cited by Prevention magazine for "Best Alternative Medical Information." It has also been cited by the World Health Organization as a model for evidence-based CAM.

- CAM on PubMed, a database developed in partnership with the National Library of Medicine, now indexes more than 467,000 scientific articles related to CAM and makes them available and accessible to health

professionals and the general public.

- For more information, see http://nccam.nih.gov/health/
- (O) (NCCAM)

Web-Accessible List of Rare Diseases Terms: Making Research Information About Rare Diseases Available to the Public: Each day, the Office of Rare Diseases (ORD) receives inquiries about specific rare diseases about which inquirers cannot find information. Over the years, ORD has maintained a list of rare diseases names from a number of sources. With the arrival of the Internet and increased Web sophistication by patients and their families, ORD began posting a list of rare diseases and conditions, with synonyms and links to federally funded databases. In 2000, ORD integrated into its database a similar European database, called Orphanet, and a list from the Engelhorn Foundation in Belgium. Since FY 2006 ORD has linked its rare diseases terms to the following databases: NLM Gateway, PubMed, Online Mendelian Inheritance in Man (OMIM), Genetics Home Reference (GHR), and ClinicalTrials.gov. The "Rare Diseases Terms" on the ORD Web site represents the most comprehensive listing of rare diseases. As such, it is a resource used by many visitors to the ORD site seeking information about rare diseases. ORD will broaden the availability of information about rare diseases on the ORD Web site by connecting a database of rare diseases questions and answers with a link to the rare diseases terms. Currently, the database contains 6,827 distinct rare diseases terms. In the last 2 years, 386 diseases were deleted because information became available that showed that the prevalence was above 200,000 in the United States, 709 new terms were added, 4,177 terms were reviewed and revised, and the available information links were expanded.

- For more information, see http://rarediseases.info.nih.gov/RareDiseaseList.aspx?PageID=1
- (O) (ODP/ORD)

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 over a billion media impressions have been achieved. The Heart Truth Road Show helps participants 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 2: *Chronic Diseases and Organ Systems*.
- (E) (**NHLBI**)

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 from 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 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (**NICHD**, NIDCR)

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 participants 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, with 50 targeting middle and high school students and 20 based in science centers and museums.

- For more information, see http://www.ncrrsepa.org
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (E) (NCRR)

Cancer.gov in Español: This 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, with pages organized around issues of greatest concern. The site will be updated using 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 2: *Minority Health and Health Disparities*.
- (E) (NCI)

NIH Senior Health Web Site: NIHSeniorHealth.gov enables the growing number of "wired seniors" to find credible aging-related health information in an online format that is compatible with their cognitive and visual needs, as evidenced by NIH-supported research. Conceived by NIA and jointly developed with NLM, the Web site includes 33 health topics developed by 12 NIH Institutes. In 2006, 760,000 visitors viewed 1.5 million Web pages on the site. To further enable older adults to locate information and participate in their own health decisions, NIA has developed a senior-friendly curriculum for people who train older adults to use computers.

- For more information, see http://www.NIHSeniorHealth.gov
- (O) (NIA)

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.

- 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 RFAs including Underage Drinking: Building Health Care System Responses (four projects awarded FY06); Impact of Adolescent Drinking on the Developing Brain; and Alcohol, Puberty and Adolescent Brain Development.

- Published A*lcohol 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 2: *Neuroscience and Disorders of the Nervous System*.
    - (E) (**NIAAA**)

NIH Health Partnership Program and Community Health Center: The Health Partnership Program (HPP) is a community-based, collaborative research program between NIH and Washington, D.C., 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, D.C., Center gives the community access to specialized care and health information, and NIH researchers 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 2: *Minority Health and Health Disparities*.
- (I) (NIAMS)

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 2: *Minority Health and Health Disparities* and *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, a 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, NLM), FDA, HRSA, CMS, and CDC.

- For more information, see http://aidsinfo.nih.gov/infoSIDA/
- This example also appears in Chapter 2: *Minority Health and Health Disparities*.
- (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 (HBCUs), 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, Alaska Native 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 2: *Minority Health and Health Disparities.*
- (I) (NLM)

The Science of Healthy Behaviors: The newest in a series of curriculum supplements distributed free of charge to teachers in grades K-12, this supplement introduces middle school students to the scientific study of behavior. It is a self-contained, teacher-ready guide to eight days of guided-inquiry science lessons that explore how behavioral and social factors influence health. The supplement is consistent with the National Science Education Standards and aligned to State standards for science, mathematics, English language arts, and health.

- For more information, see http://science.education.nih.gov/customers.nsf/MSHealthy.htm
- (E) (**OBSSR**, NINR, OSE)

Rapidly Responding to Time-Sensitive Issues

Helping Patients Who Drink Too Much: A Clinician's Guide: In January 2007, NIH issued an update to its 2005 edition of the 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 nonspecialty 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 2: *Chronic Diseases and Organ Systems.*
- (E) (NIAAA)

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 2: *Chronic Diseases and Organ Systems.*
- (E) (**NIAAA**, NIDA)

Science of Dissemination and Implementation: Relatively little is known about how to ensure that the lessons learned from research inform and improve the quality of health and human services in the population at large. The goals of the program announcement, *Dissemination and Implementation Research in Health, and conference, Building the Science of Dissemination and Implementation in the Service of Public Health* (September 2007), are to support innovative approaches to identifying, understanding, and overcoming barriers to the adoption, adaptation,

implementation, and maintenance of evidence-based practices by health care providers, insurers, policymakers, and the public.

- For more information see http://grants.nih.gov/grants/guide/pa-files/PAR-07-086.html
- For more information see http://obssr.od.nih.gov/di2007/index.html
- This example also appears in Chapter 3: *Clinical and Translational Research.*
- (E) (**NCI**, NHLBI, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIMH, NINR, OBSSR, ODS)

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.

- December 2002: "Research Partnership Awards for Rapid Response to College Drinking Problems." Five U01 (cooperative agreement) 5-year grants were awarded.
- June 2003: "Rapid Response to College Drinking Problems." Fifteen 3-year grants were awarded.
    - 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: *Chronic Diseases and Organ Systems*, Chapter 3: *Epidemiological and Longitudinal Studies*, and Chapter 2: *Life Stages, Human Development, and Rehabilitation.*
- (E) (NIAAA)

Recognizing Problems and Taking Action

National Network of Libraries of Medicine: With more than 5,800 full and affiliate members, the Network 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 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 http://nnlm.gov/
- This example also appears in Chapter 2: *Minority Health and Health Disparities.*
- (I) (**NLM**)

Health Disparities Research Forum: NIH will be convening a 3-day forum in the spring of 2008. The purpose of the forum is to highlight the collective progress of NIH and its HHS government partners, grantees/academicians, community organizations, and health care providers in implementing programs and strategies in the major priority areas, identified in the first *NIH Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities.* The objectives of the Research Forum are to:

- Identify best practices, challenges, programs, and existing or potential gaps and practices in research initiatives, strategies, and funding,

- Promote research partnerships by identifying opportunities to strengthen partnerships, by establishing new partnerships within NIH and across HHS, within and between academic institutions and researchers, and within and between community organizations and health care providers, and
- Strengthen the health disparities research collaborations at the government, academic, and community levels.

    - (O) (NCMHD)

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 trained to implement them. This work is occurring through the National Drug Abuse Treatment Clinical Trials Network (CTN) at NIH, which involves practitioners from community treatment programs (CTPs) 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 CTPs 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: *Chronic Diseases and Organ Systems*, Chapter 3: *Clinical and Translational Research*, and Chapter 2: *Neuroscience and Disorders of the Nervous System.*
- (E) (NIDA) (GPRA Goal)

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. While 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 2: *Minority Health and Health Disparities.*
- (E) (**OBSSR**, AHRQ, NCI, NHLBI, NIA, NIBIB, NICHD, NIDCD, NIDCR, NIEHS, NIMH, NINR, NLM)

Outreach to the Scientific and Research Communities

The NIMH Outreach Partnership Program: This program is a vital element in the broad NIH outreach effort to deliver science-based information to the public, health professionals, constituency groups, and all interested stakeholders.

- For more information, see http://www.nimh.nih.gov/outreach/partners/index.cfm
- (E) (NIMH)

Partners in Information Access for the Public Health Workforce (PH Partners): PH Partners, a 12-member public-private collaboration initiated by NIH, Centers for Disease Control and Prevention, and National Network of

Libraries of Medicine assists the public health workforce to make effective use of electronic information sources. The Partners Web site (PHPartners.org) provides unified access to public health information resources produced by all members of the Partnership, as well as other reputable organizations. In FY 2006, the Web site was expanded with more than 400 new links and two new categories: Fellowships and Upcoming Meetings. One of the most popular resources on the site is the Healthy People 2010 Information Access Project.

- For more information, see http://phpartners.org/
- (I) (NLM)