

SIGNIFICANT ITEMS (SIs)

FY 2012 Senate Appropriations Committee Report
and
FY 2012 Conference Committee Report

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National Cancer Institute (NCI)

Senate Significant Items

Item

Breast Cancer. - The Committee notes that triple-negative breast cancer is poorly understood and has a disproportionate prevalence among African American women. The Committee encourages NCI to increase research and awareness of this disease, and to advance prevention, detection, diagnosis, care, and treatment. The Institute is urged to collaborate with ORWH, NIMHD, the Office of Minority Health, and the Office of Women's Health in these efforts. (p. 86)

Action taken or to be taken

Triple-negative breast cancer lacks three "receptors" known to fuel most breast cancers, estrogen receptors, progesterone receptors and human epidermal growth factor receptor 2 (HER2). NCI is supporting research to provide greater insights into the biological basis underlying triple-negative breast cancer among high-risk, racially/ethnically diverse, and underserved populations. One project focuses on epigenetic factors, i.e., environmental factors such as diet or exposure to carcinogens or hormones that may alter genomic function. The research will focus on pregnancy-associated post-partum breast cancers (often triple negative) compared with non-pregnancy-associated breast cancers in Hispanic women. Findings may also serve as a foundation for the development of biomarkers and targeted therapies. Another study is exploring the interplay between mammary fat tissue and breast cancer health disparities, which may lead to new insights into prevention strategies and/or therapeutic alternatives for overweight/obese women, especially among African Americans and Latinas. A third study is testing an immunotherapeutic strategy with potential to improve cancer treatment for patients who are resistant to other, more conventional therapies.

NCI is also supporting research on triple-negative breast cancer through proceeds from sales of the Stamp for Breast Cancer Research. One effort aims to identify distinct subtypes of triple-negative breast cancers and potential therapeutic targets. Another uses genomic technology to examine triple-negative breast cancers from Caucasians, Hispanics, and African Americans to explore the differences across ethnic groups and to examine connections to differences in tumors across populations. A third project will explore a gene-silencing protein called EZH2 that is elevated in triple-negative breast cancers and assess it as a possible prognostic tool. Finally, the NCI's Early Detection Research Network is undertaking a project to identify blood markers for triple-negative breast cancer to identify women age 40 and older who may be at high risk for the disease.

Other related research includes two prevention trials in women with a history of hormone-receptor negative breast cancer. One study is testing a method to reduce the level of a protein called poly-adenosine-ribose polymerase (PARP) by using an inhibitor called ABT-888. PARP inhibitors have been identified as agents that could further disrupt DNA repair in breast cancer cells, rendering them particularly vulnerable to certain chemotherapy treatments. The other study is exploring ways to reduce the level of a protein called Ki67 that is associated with cancer cell growth by using increasing doses of a green tea component called Polyphenone E.

NCI works with trans-NIH groups to disseminate and coordinate information about health disparities research, pursue collaborative research efforts, and co-fund investigators studying health disparities and cancer, as well as participating in HHS-wide efforts to address minority and women's health concerns. NIMHD Centers of Excellence Program conducts research, training, and community outreach around issues of minority health and health disparities. The Center of Excellence in Eliminating Disparities at the University of Illinois-Chicago is evaluating the effectiveness of a hospital-based patient navigation intervention strategy on the adequacy of diagnostic and treatment services for breast cancer care among underserved women. The primary research outcome will be treatment adequacy and adherence to follow-up care in women with abnormal mammograms. In addition, in FY2011, NIMHD funded an NCI intramural scientist to investigate triple-negative breast cancer that is prevalent in younger African American women. Findings from these studies will inform strategies for early screening and treatments for these women.

Item

Health Decisionmaking. - The Committee commends NCI for its efforts to understand how the ability to comprehend and use numerical information affects health decisionmaking, as low numerical skills may not only distort perception of risks and impair risk communication, but may also impede treatment. (p. 86)

Action taken or to be taken

Advances in cancer prevention, screening, treatment and end-of-life care, coupled with advances in bioinformatics, have created a wide array of health care options and sources of medical information. NCI funds research that examines, among other factors, cognitive and affective processes underlying decision making; basic decision-making processes involved in the initiation and long-term maintenance of healthy lifestyle behaviors; and health-related numeracy—how people use, process, and attach meaning to health-related numeric information.

To better understand health behaviors and their underlying processes, NCI experts and external scientists work together to examine cognitive, affective, and social processes involved in health communication and risk perception. This effort enables cancer-related information such as risk assessments to be presented to patients, providers, and the public in a user-friendly, easily processed, and informative manner. For example, the Health Information National Trends Survey (HINTS) (<http://hints.cancer.gov/>) is an NCI project that collects data on the American public's need for, access to, and use of cancer information, with special emphasis on ethnic minority populations. It provides a unique set of data that enables investigators to examine the relationship between health communication and cancer-related knowledge, attitudes, and behaviors.

NCI supports centers that conduct transdisciplinary cancer communication research aimed at directly contributing to improved health outcomes and quality of life for individuals. The centers facilitate rapid advances in knowledge about cancer communications, develop effective interventions, translate theory and programs into practice, and train health communication scientists.

NCI also works closely with NIH to lead the trans-NIH Basic Behavioral and Social Science *Opportunity Network* (OppNet). OppNet supports research including analyses of theoretical issues of numeracy, risk taking and risk perception, and cognitive mechanisms that link the framing of choices to decision outcomes in general.

Item

Health Services Research. - The Committee commends NCI for its efforts to determine how well state-of-the-art cancer care is actually delivered. Ongoing health services data collection and surveillance programs represent an important contribution to cancer surveillance and the efforts to understand and improve clinical and community practices. NCI is strongly urged to maintain support for ongoing activities that advance cancer prevention and early detection research, including data collection infrastructure that can contribute to measuring the delivery and outcome of services, and comparative effectiveness research. (p. 86)

Action taken or to be taken

NCI recognizes the importance of health services research to understand and improve cancer prevention, early detection, cancer care delivery, and health outcomes. Through a number of initiatives involving networks and consortia and infrastructure support, NCI research is making vital contributions to measuring health services and patient-centered outcomes research (PCOR). PCOR includes research that helps people to make informed health care decisions, allows their voice to be heard in assessing the value of health care options, and answers patient-focused questions.

The NCI Surveillance, Epidemiology, and End Results (SEER)-Medicare database combines two large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer. The SEER-Medicare database is a unique population-based source of information that can be used for an array of epidemiological and health services research, including patterns of care, utilization of cancer tests, and efficacy of cancer treatment.

The NCI Health Maintenance Organization (HMO) Cancer Research Network (CRN) consists of the research programs, enrolled populations, and data systems of 14 HMOs nationwide that, collectively, provide care to almost 11 million individuals. As a reflection of its commitment to improving quality of care, the Agency for Healthcare Research and Quality is cooperatively supporting the CRN with NCI. CRN research focuses on the characteristics of patients, clinicians, communities, and health systems that lead to the best possible outcomes in cancer prevention and care. The CRN allows for large, multi-center, multidisciplinary intervention research that addresses the spectrum of cancer control, including studies of prevention and early detection. Reissuance funding for the HMO CRN is planned for FY12.

In 2011, NCI funded seven cooperative research centers and one statistical coordination center through the Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) initiative. Screening for cancers in the large population of people who do not have obvious cancer symptoms represents a major undertaking in the United States. Studies are needed to identify interventions that use current and emerging technologies to maximize the

detection of clinically relevant cancers while limiting harms and that assure equitable access across diverse screening delivery settings and geographic regions.

Item

Liver Cancer. - The Committee urges NCI to increase its efforts in the area of liver cancer, particularly by creating a Specialized Program of Research Excellence [SPORE] for this disease and by funding projects focusing on pathogenesis, detection and/or therapeutics. (p. 86)

Action taken or to be taken

Liver cancer, or hepatocellular carcinoma (HCC), is the third leading cause of cancer deaths worldwide, and incidence for men has been slowly rising over the past twenty-five years. Research aimed at diminishing the human impact of this cancer is a priority, and NCI continues to leverage its resources to understand the etiology and pathogenesis of HCC, as well as to identify ways to develop new prevention, detection, and treatment approaches. New data on HCC that will inform future research directions are anticipated based on the inclusion of HCC into the list of cancers to be studied in The Cancer Genome Atlas (TCGA), a large-scale effort to compile a comprehensive, detailed catalogue of the genetic changes that result in cancers.

Hepatitis B and hepatitis C infection appear to be the most significant causes of HCC worldwide, and NCI supports research on screening and vaccination in high-risk groups as a way to reduce HCC incidence and mortality rates. Other efforts, including the University of Kentucky's Gastrointestinal Cancer (GI) Specialized Program of Research Excellence (SPORE), are focused on hepatitis C and development of HCC. Two large Phase III NCI-supported clinical trials in HCC that seek to build on advances with sorafenib, a biologically targeted agent with demonstrated activity in HCC, are underway, in addition to early clinical research examining other targeted agents. To further augment these efforts, NCI continues to encourage investigators to submit applications for an HCC-focused SPORE for peer review and consideration for funding.

In addition to the more traditional risk factors of alcohol and infection with hepatitis B and/or hepatitis C, the role of other factors such as obesity, diet, and diabetes are being examined. Recent NCI studies have shown that over 40% of HCC cases diagnosed in the U.S. are unexplained and not related to known risk factors such as alcohol, hepatitis infection, or rare genetic disorders. Previous NCI analyses among large U.S. cohorts have found independent association between liver cancer and diabetes, metabolic syndrome, red meat intake, and saturated fat, suggesting a role of overweight or obesity in liver cancer risk. To explore this lead, NCI researchers are pooling data from sixteen large U.S. studies and examining the roles of diabetes, metabolic disorders, and obesity in liver cancer risk. Inflammatory markers will be examined to evaluate whether obesity increases the risk of liver cancer through immune-mediated pathways. This study is the only prospective evaluation of liver cancer risk factors and the largest U.S. study of liver cancer to date. Identifying other key liver cancer risk factors may provide important evidence that can inform development of appropriate interventions and prevention efforts. Another NCI effort is focusing on identifying medications, such as diabetes drugs, anti-inflammatory drugs, or statins, that might be related to a decreased risk of HCC.

NCI intramural investigators are conducting several novel HCC studies ranging from a Phase I study targeting multiple genes and incorporating nanotechnology to interfere with gene expression to research aimed at the identification and eradication of liver cancer stem cells. Researchers have also identified changes in lipid metabolism that occur with HCC, a finding that may provide new insights into HCC pathobiology and also be used as a biomarker to evaluate the efficacy of treatment. NCI's Gastrointestinal Steering Committee's Hepatobiliary Cancer Task Force continues its collaborative efforts to develop new strategies for the prevention, detection, and treatment of HCC.

Item

Lung Cancer. - The Committee remains concerned by the high morbidity and mortality rates of lung cancer, particularly the increased lung cancer rates among women and the high incidence among African American men. NCI is urged to enhance support for research in these areas. (p. 86)

Action taken or to be taken

NCI shares the Committee's concerns, and because accelerating efforts to avoid tobacco use is the area of cancer prevention with the potential to yield the largest public health benefit for all populations, NCI funds a significant portfolio of smoking cessation research and community resources, such as the Smokefree Women campaign that provides evidence-based cessation guidance tailored to the needs of female smokers, and research focused on reducing the unequal burden of tobacco on African-American men and other at-risk groups. Thanks to the concerted efforts by the NCI and many other organizations, incidence and mortality from lung cancer in males have shown a progressive decrease for more than 15 years. Over the past decade, the rates of decline in lung cancer incidence and mortality rates have been somewhat greater among African American males than among white males, although the overall rates remain higher for African American males. Mortality data from 2007, the latest year for which full analysis is available, indicate that lung cancer mortality in women has now also started to decline after having been level for the past decade.

A key component of NCI's lung cancer research portfolio includes efforts to improve screening and diagnosis. NCI recently released initial results of the National Lung Screening Trial (NLST), a randomized national study of over 53,000 current and former heavy smokers ages 55 to 74, 41 percent of whom were women, that examined the utility of helical computed tomography (CT) in detection of lung cancer. The results demonstrated that screening with low-dose helical CT, as compared to standard chest X-ray, resulted in 20 percent fewer lung cancer deaths. This finding implies that helical CT screening for high-risk individuals, as defined in the trial, can save lives, and additional analyses of the data are expected to provide scientists with a deeper understanding of this disease, its causes, and other potential ways to reduce its burden.

NCI-supported basic research has enabled a vastly accelerated understanding of the molecular and genetic mechanisms of many cancers, including lung cancer. For example, the discovery of the epidermal growth factor receptor (EGFR) mutation, found mainly in non-small cell lung cancer (NSCLC), which accounts for the majority of lung cancers, can be used as a biomarker that generally predicts a positive response to tyrosine kinase inhibitors such as erlotinib. Other

advances include identification of EML4-ALK, a mutation found in approximately 5 percent of NSCLC patients, and the development of crizotinib, a targeted therapy that showed dramatic response rates in clinical trials, leading to rapid approval for locally advanced or metastatic NSCLC.

Additional molecular profiling of lung cancer tumors is being pursued through The Cancer Genome Atlas (TCGA), in which many researchers are working together to distinguish patterns of gene changes between different forms of lung cancer, specifically adenocarcinoma and squamous cell carcinoma, as well as genomic changes between smokers and non-smokers. Further analyses could suggest a possible utility in lung cancer for drugs already approved, or may lead to the development of new drugs against these targets.

Item

Melanoma. - The Committee urges more research on melanoma that will identify and develop molecular markers to aid accurate diagnosis of the primary tumor; prognostication that will determine extent and type of treatment; and prediction of treatment response. The Committee commends NCI for the inclusion of melanoma in The Cancer Genome Atlas; however, in view of the relative scarcity of melanoma biospecimens available for this effort, additional resources are needed to facilitate specimen collection. Given the rising incidence rates of melanoma, the Committee encourages NCI to support research directed at the biology of tumor initiation including UV radiation as a carcinogen, host risk factors and risk reduction strategies. The Committee continues to urge NCI to promote mechanisms of collaboration between industry, the extramural program and foundations that will accelerate translational and clinical research as outlined in the strategic action plan, including annotated specimen collection from key trials independent of sponsorship and novel trial designs to accommodate testing agents contributed by more than one company. The Committee requests an update on these requests in the fiscal year 2013 congressional budget justification. (p. 86-87)

Action taken or to be taken

There have been exciting advances in melanoma research in the past year, and NCI supports a broad melanoma research portfolio of basic research and clinical trials testing new therapies alone or in combination with other agents. Through its Clinical Trials Cooperative Groups, NCI is supporting pivotal studies incorporating translational research to advance the characterization of molecular targets, biomarker development, and integration of molecular imaging. In 2011, results of two Phase II clinical trials of new therapies for advanced melanoma were reported, confirming two new valuable treatment options for advanced melanoma. The first study showed tumor regression in patients treated with vemurafenib (PLX 4032), a recently approved targeted inhibitor of the B-Raf gene. For some patients, the drug has dramatically extended response time as compared to other therapies. But because many patients eventually build resistance to the drug, NCI is sponsoring additional research geared at patients whose disease stops responding, offering trials examining combination therapies targeted at specific genetic pathways. The second study showed increased survival extending several years post-treatment in patients treated with ipilimumab, a recently approved immunotherapy. NCI is supporting additional studies with the drug and is collaborating with industry to sponsor a Phase III with early stage melanoma patients who are at high risk of relapse.

The Cancer Genome Atlas (TCGA) began sequencing more than 200 melanoma cases in October 2011. Completion of the genomic sequencing of skin cancers has revealed several potential targets for melanoma therapy including genes affecting tumor growth and clinical outcome in melanoma, and an activator in a key-signaling pathway involved in human melanoma. NCI research also suggests that targeted interventions immediately after sunburn might protect against UV radiation-induced melanoma, and explores potential therapeutic targets.

NCI provides biospecimen resources through the Cooperative Group Tumor Banks, which receive and distribute cancer specimens linked to NCI clinical trial data; the Cooperative Human Tissue Network, which provides specimens to investigators for biomarker discovery and validation; and the Melanoma Progression Tissue Microarray, to investigate differences in expression of markers in various stages of progression.

NCI-funded investigators also participate in the Breakthrough Consortium, a collaboration with advocates and industry partners to advance research in combination drug trials. In September 2011 NCI also convened a meeting to discuss collaborative opportunities with several melanoma research advocacy organizations, and this effort is ongoing.

Item

Metastasis to Bone. - The Committee urges additional research on how to repair bone defects caused by cancer cells. Translational research is also needed to understand the impact of metastasis on the biomechanical properties of bone and the mechanisms by which bone marrow and tumor-derived cells can influence metastatic growth, survival and therapeutic resistance. (p. 87)

Action taken or to be taken

NCI is funding research projects investigating the biological processes in metastasis and identifying methods to prevent or interrupt those processes. At the basic biologic level, NCI is supporting various approaches to addressing metastasis, such as efforts to understand why and how tumor cells in the bone marrow can be unaffected by chemotherapy drugs, and developing experimental models of prostate cancer bone metastases. NCI-supported researchers are also working to identify inhibitors of bone metastasis by focusing on a tumor suppressor gene called maspin. Clinical studies have suggested that the level of activity of maspin may have an inverse association with disease progression, i.e., maspin expression is lower in the presence of invasive metastatic carcinomas and higher in patients with longer survival. In experimental models, maspin inhibits metastasis to the bone and sensitizes prostate cancer cells to drug-induced cell death.

There have been several advances in the last year which may lead to more effective treatment options and improved outcomes for metastatic cancers. Increasingly, the evidence suggests that metastasis occurs as a coordinated process between tumor cells and host cells through a process of inflammation. NCI researchers are actively investigating the immune/inflammatory role of transforming growth factor-beta (TGF β), a growth factor produced in large quantities by many tumor types, and exploring the anti-metastasis effect of TGF β antagonist therapies.

NCI researchers have also developed a targeted therapy to inhibit expression of CXCR4, a chemokine receptor that plays a role in the development of metastatic disease in bone, sarcoma, and lung. Other research includes using the drug cediranib to inhibit bone and brain metastasis in preclinical models of advanced prostate cancer, and using a peptide called COG11 to interrupt a process that stimulates cellular growth along pathways that promote metastasis. These types of research could lead to the development of a widely applicable anti-metastasis therapy.

NCI-supported research is also studying bone marrow for signs of microscopic metastatic disease to define the role of bone marrow-derived cells as biomarkers and prognostic tools for predicting disease recurrence or metastasis. Related research is exploring the association between survival and the presence of tumor cells in the bone marrow of breast cancer patients. NCI is also researching the effect of hormones on certain types of cancers, and is supporting a Phase II trial investigating the effects of an anti-androgen therapy in patients with resectable prostate cancer, which frequently metastasizes to bone.

NCI supports several research projects focused on bone repair and the prevention of bone loss. Projects include an examination of bisphosphonates to prevent the loss of bone mass in prostate cancer-induced bone disease and metastatic breast cancer. One study explores whether chemotherapies with bone-targeting bisphosphonates may reverse the deterioration of bone associated with cancer. The goal of this research is to deliver effective anti-cancer therapies to bone while also providing bone-protection agents. Another study aims to measure the effect of bisphosphonates on bone turnover in patients with metastatic breast cancer and to identify early interventions to prevent fractures and other skeletal events. NCI also supports a study to develop a new generation of lipophilic bisphosphonates, a class of bisphosphonates that are more effective in inhibiting tumor cell growth, including compounds that can bind directly to bone.

Item

Pancreatic Cancer. - The Committee commends NCI on its fiscal year 2011 Action Plan for Pancreatic Cancer, which marks an important first step to making a targeted research investment in this deadly disease. As the plan recommends, the Committee urges NCI to put in place a long-term, comprehensive strategic plan; move forward with requests for applications or program announcements specific to pancreatic cancer; and include more experts in pancreatic cancer on scientific review panels in fiscal year 2012. In addition, earlier this year NCI reported to the Committee that extramural research staff has been empowered to propose exceptions for promising pancreatic cancer research proposals that may not otherwise be funded, and that the Institute has made it a priority to identify novel research ideas. The Committee requests an update in the fiscal year 2013 congressional budget justification on the use of exceptions as well as a description of novel research ideas being pursued in relation to pancreatic cancer. (p. 87)

Action taken or to be taken

NCI is continuing to move forward with its strategic investment into pancreatic cancer as reported in the FY2011 Action Plan, supporting a varied portfolio of ongoing research. Several new research projects that fall under this strategic plan, such as efforts by the Pancreatic Cancer Cohort Consortium to examine the function of four genomic variants associated with pancreatic

cancer identified by earlier genome-wide association studies (GWAS), have been initiated. Another project is a 950-patient Phase III trial in adjuvant therapy for pancreatic cancer being conducted by the NCI Clinical Trials Cooperative Groups. The study is the largest of its kind, designed to answer the fundamental question about the value of adding radiation to chemotherapy, with or without the addition of the targeted drug erlotinib. NCI is also supporting immunotherapy research for advanced pancreatic cancer, including one trial of the targeted drug ipilimumab and another studying the effect of the administration of tumor-infiltrating lymphocytes isolated from surgically removed pancreatic cancer metastases.

Additional NCI-supported research includes analysis of the recent findings that losartan, a drug commonly used to treat hypertension, has been shown to “open” compressed tumor vessels and make dense pancreatic cancer cells more permeable to anti-cancer drugs. This development offers a rapidly translatable strategy to improve the treatment of pancreatic cancer, and efforts are underway to test whether adding losartan to standard therapy can improve survival. Other research includes analysis of biospecimens from pancreatic cancer cohort studies to explore possible associations between pancreatic cancer and diseases such as diabetes, metabolic disorders, and obesity, and studies exploring disease origins, inflammation and disease progression, and ways to target molecular pathways for therapy.

The process by which NIH grant applications are evaluated is centered on the review of applications by NIH standing study sections that are comprised of a wide range of scientific experts. The groups are not arranged by groups of diseases, or organ sites; rather, study sections are formed around the scientific approach of the research being proposed and focus on the disciplines relevant to the research proposals being reviewed, e.g. epidemiology, genomics, therapeutics development, populations, behavior. The groups are populated by productive investigators with expertise in those areas.

The NCI scientific leadership, in an effort to strengthen our ability to fund the most promising and important new research questions, examines grant applications and their review statements to ensure a balanced grant portfolio and recognition of and investment in highly original research proposals for all cancer types, including pancreatic. Using this approach, applications that score exceptionally well in the peer review process – within the 7th percentile – almost always receive funding. Applications that score well, but outside of the 7th percentile, are placed in a “zone of uncertainty” and may receive further review by the NCI’s scientific program staff and leadership, allowing NCI to take advantage of the most promising scientific opportunities.

This additional layer of consideration has enabled NCI to identify and approve FY 2011 funding for various promising pancreatic cancer research proposals that may not have otherwise been funded. These include 17 newly competing grant proposals and 59 renewals of grants focusing exclusively on pancreatic cancer research, as well as 25 proposals focused in part on pancreatic cancer research.

Item

Pediatric Cancer. - The Committee notes that childhood cancer research accounts for less than 5 percent of the Institute's annual budget and encourages NCI to increase that amount, as cancer

remains the leading cause of disease related death in children. More effective and less toxic treatments are needed. (p. 87)

Action taken or to be taken

NCI must give full attention to the clinical consequences of every cancer type, and we also must be responsive to the opportunities and ideas that seem likely to offer the best chances of making discoveries that bring us closer to understanding and reducing the burden from all cancers. While much of our research, especially our clinical and translational research, is focused on specific cancers, NCI does not apportion a set amount of funding to be used for any specific type of cancer, including pediatric cancers. Funding levels are dependent on the number of research project grant applications and the quality of those proposals, as determined by rigorous peer review.

In recent history, about 4% of the NCI's total funding has been invested specifically in pediatric cancer research efforts across the nation. In fiscal year 2009, NCI provided \$192.8 million for pediatric cancer research and an additional \$47.2 million from its American Recovery and Reinvestment Act (ARRA) allotment. In fiscal year 2010, NCI invested \$199.8 million in this research, with an additional \$13.2 million from ARRA funds. In fiscal year 2011, NCI's estimated investment was \$197 million. However, the 4% estimate does not reflect the NCI's investment into basic research on cancer mechanisms that contributes heavily to the understanding of all cancers.

NCI supports a comprehensive pediatric cancer research program, ranging from basic molecular projects through preclinical testing and clinical trials to epidemiological studies to identify potential factors associated with childhood cancer development. Pediatric cancer features prominently in our most innovative and high-profile research efforts such as the TARGET (Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatment) Initiative, a public-private partnership harnessing genomics technology to identify molecular targets to diagnose and treat childhood cancers more precisely, effectively, and safely than ever before. The NCI-supported Pediatric Preclinical Testing Program (PPTP) systematically generates pre-clinical data about promising new agents and combinations of agents for childhood cancers. Research underway through NCI's intramural pediatric oncology program spans basic, translational, and clinical trials focused on drug development of targeted agents, genomics, immunotherapy, imaging research, and psychosocial research. Studies also continue to examine increased risk of subsequent cancers and late toxicity of treatment in survivors of childhood cancer. NCI investigators and extramural collaborators are conducting a follow-up study of long-term childhood cancers to evaluate subsequent cancers and several chronic disease outcomes.

NCI funds significant extramural research efforts through the NCI Cooperative Children's Oncology Group (COG), an NCI Cooperative Group that develops and coordinates pediatric cancer clinical trials that are available at over 200 member institutions, including cancer centers throughout the United States and Canada. NCI also leverages resources by partnering to conduct international trials, which allows researchers to learn more quickly whether new treatments are more effective than current treatments. Finally, an important feature of the NCI research program is its work addressing the special issues faced by childhood cancer survivors. NCI is supporting

the Childhood Cancer Survivor Study (CCSS), a collaboration of 27 institutions working to learn more about the late effects of childhood cancer treatment.

Item

Slow-Growing Children's Brain Tumors. - Two primary roadblocks to basic research on pediatric low-grade astrocytoma [PLGA] brain tumors have been identified: a shortage of viable tissue samples and the lack of a mouse model. The Committee urges NCI to establish research priorities that address the shortage of tissue samples by incentivizing hospitals and medical institutions to centralize and share tissue samples. The Committee also urges NIH to examine possible solutions to address the lack of a mouse model for PLGA brain tumors. The Committee requests an update on these issues in the fiscal year 2013 congressional budget justification. (p. 87)

Action taken or to be taken

Major advances in understanding the biology of PLGA have been achieved over the past five years, and because of these advances clinical research teams are now poised to translate these findings into new therapeutic options. The most significant research advance is the recognition that most PLGA cases have genomic alterations involving a gene called BRAF, and preclinical models that will allow identification of promising candidate treatments are being developed. The NCI-supported Pediatric Preclinical Testing Program has developed a model for a subtype of PLGA with a BRAF mutation known as BRAF V600F, and identified a targeted agent called selumetinib that is effective against the model. Based in part on these preclinical results, the NCI-supported Pediatric Brain Tumor Consortium is conducting a Phase I trial of selumetinib in children with PLGA who have progressed after receiving radiation therapy. Other research teams have developed preclinical models for this same BRAF V600F subtype of PLGA and are using these models to identify novel agents effective against this disease. In addition, preclinical models of a type of PLGA based on alterations in the NF1 gene (the gene that causes neurofibromatosis 1) have been used to identify new therapeutic targets for PLGAs with NF1 alterations.

Mouse models of human brain cancer have been successfully developed through NCI-supported research, including efforts at several extramural grantee institutions with core activities supporting development of these brain cancer models. To further advance this research area, NCI-supported investigators widely share research resources including brain cancer cell lines, tissues, and animal models with research institutions in the United States and abroad.

Future advances in understanding the genomic alterations of PLGAs are anticipated, as genome sequencing of PLGAs is being undertaken by a team of German pediatric brain tumor researchers through the International Cancer Genome Consortium (ICGC), of which NCI is also a partner. The ICGC collaborative effort allows member institutions to prioritize research efforts and avoid duplication. For example, while German researchers are taking the lead in collecting and analyzing PLGA tumor tissue samples, the NIH Cancer Genome Atlas (TCGA), which analyzes the complete genomes of various cancer types, is taking the lead on collection and analysis of other brain cancer types. TCGA will also be moving toward collecting available

tissue samples from pediatric and adolescent astrocytomas such as PLGA to further advance research of this pediatric cancer.

Conference Significant Items

Item

Neuroblastoma. - The conferees note the promising results of a recent clinical trial using a chimeric antibody to treat newly diagnosed neuroblastoma patients. The conferees support efforts to facilitate access to this new therapy for relapsed patients and request an update in the fiscal year 2013 congressional budget request. (p. 38)

Action taken or to be taken

Neuroblastoma, which occurs primarily in infants and young children, is a cancer that develops in the tissues of the sympathetic nervous system. Each year there are approximately 650 new cases in the United States, of which 40% to 50% have high risk disease. ch14.18 is a chimeric mouse/human monoclonal antibody produced by the National Cancer Institute's (NCI's) Biopharmaceutical Development Program (BDP). It targets GD2, a molecule that is highly expressed on the surface of neuroblastoma cancer cells, leading to activation of the immune system against GD2-expressing neuroblastoma cells. Phase 3 clinical trial results reported by Dr. Alice Yu and her Children's Oncology Group (COG) colleagues have shown that an immunotherapy regimen that includes ch14.18 improves the rate of survival without disease recurrence for pediatric patients with neuroblastoma.

NCI has entered into a cooperative agreement with the United Therapeutics Corporation to manufacture ch14.18 and is collaborating with the company to obtain regulatory approval for the production of ch14.18 for the treatment of high risk neuroblastoma. In the meantime, NCI continues to be the sole source of ch14.18 for children with high risk neuroblastoma. Until recently, the supply of ch14.18 was so limited that the agent could only be made available to treat the subset of newly diagnosed patients for whom the agent was shown effective in the COG phase 3 clinical trial. However, sufficient quantities of ch14.18 have now been manufactured by NCI so as to allow clinical trials in children with relapsed neuroblastoma to proceed.

NCI is working with researchers in the New Approaches to Neuroblastoma Therapy (NANT) Consortium and with COG neuroblastoma researchers to develop clinical trials for relapsed neuroblastoma patients. These clinical trials will evaluate novel ways to more effectively use ch14.18 to treat children with high-risk neuroblastoma, and they are anticipated to be open and enrolling patients by the fall of 2012. Importantly, NCI has also developed a process by which children with relapsed neuroblastoma who have not previously received ch14.18 and who have achieved a "minimal disease state" (through response to other therapy) can receive ch14.18 immunotherapy outside of a clinical trial. More information is available at (http://ctep.cancer.gov/branches/pmb/ch14_18_special_exception.docx).

National Heart, Lung, and Blood Institute (NHLBI)

Senate Significant Items

Item

Asthma. - NHLBI is urged to advance more effective life-saving and life-enhancing treatments for asthma and to collaborate with the FDA, NIAID, NICHD, NIMHD, and the Office of Minority Health in this regard. The Committee notes that the prevalence and burden of asthma are high among African Americans, Latinos and other communities of color, as well as children. The Committee urges NHLBI to examine the impact of long-acting medications and prescribed steroids on overall health, growth and development of children. (p. 88)

Action taken or to be taken

The National Heart Lung and Blood Institute (NHLBI) recently launched two programs - Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases and Phase II Clinical Trials of Novel Therapies for Lung Diseases - to accelerate development and testing of new agents for treating asthma and other lung diseases. The Severe Asthma Research Program was renewed and expanded; it will conduct long-term follow-up of patients to consider the mechanisms of severe asthma and factors that influence response to therapy. The NHLBI AsthmaNet addresses clinical questions about management of adult and childhood asthma and examines new applications of existing drugs for asthma control.

Collaborations among NHLBI, NIAID, NICHD, NIEHS, and NIMHD facilitate comprehensive exploration of the many dimensions of asthma to better understand interactions among genes, immune function, lung function, and environmental exposures (infections, pollution, allergens, and psychosocial stresses) that lead to asthma inception and progression. These research programs may yield new treatment approaches to improve asthma control and perhaps reverse the course of asthma. These NIH components also participated in an NIH workshop to develop a coordinated research agenda on asthma prevention. In addition, they participated, along with AHRQ and the FDA, in a large asthma outcomes workshop that sought to promote standardization of outcome measures and enable cross-study comparisons and data sharing.

A broader collaborative Coordinated Federal Action Plan to Reduce Racial and Ethnic Asthma Disparities is being developed within the trans-agency Task Force on Environmental Risks and Safety Risks to Children including the Office of Minority Health. The plan will be a blueprint for coordinating research, surveillance, policy, and public health interventions that promote comprehensive asthma management programs for children at highest risk of having poor asthma outcomes. NHLBI and NIAID support extensive research on asthma in racial and ethnic minorities. NHLBI epidemiologic studies examine the impact of environmental, genetic, and psychosocial stresses affecting pregnant women on the development of asthma in their children; clinical research targets minority communities (e.g., NIAID's Inner City Asthma Consortium); and NHLBI behavioral research evaluates innovative methods using web-based technologies, electronic health records, mobile phones, and peer coaching to increase adherence to clinical practice guidelines by health care providers and patients alike in disadvantaged communities. The NHLBI National Asthma Education and Prevention Program recently launched the National Asthma Control Initiative to integrate efforts across health care providers, schools, pharmacies

and families to improve asthma management in local communities, especially those experiencing a high asthma burden.

NHLBI sponsors several research programs to examine the impacts of long-term medications on children's health and development. The Childhood Asthma Management Program has followed over 1000 children for 18 years to examine the long-term effects of daily inhaled corticosteroids or nedocromil on lung growth, height, overall quality of life and psychosocial development, and the progression of asthma severity. AsthmaNet is studying the effectiveness of asthma medications in children as well as potential effects on growth and development.

Item

Cardiovascular Disease. - The Committee continues to place a high priority on research related to heart disease, stroke and other forms of cardiovascular disease and remains concerned that NIH still spends less than 8 percent of its budget on our Nation's No. 1 and most costly killer. The Committee strongly urges NHLBI to significantly enhance its investment and further stimulate interest in multidisciplinary and interdisciplinary basic, clinical, translational, and prevention cardiovascular disease research, including its risk factors, using all appropriate mechanisms. In addition, the Committee urges the prompt implementation of priority initiatives outlined in its Division of Cardiovascular Diseases Strategic Plan. NHLBI is also encouraged to increase its attention to the impact of cardiovascular disease on ethnic minorities such as Native Hawaiians and Asians. (p. 88)

Action taken or to be taken

The National Heart Lung and Blood Institute (NHLBI) supports a robust portfolio of research on cardiovascular disease (CVD) ranging from basic studies of underlying pathological mechanisms to large trials that address clinical issues, including the comparative effectiveness of established treatments in real-world settings. Some of this work is conducted with other NIH ICs (including NIDDK and NINDS). About 63% of the NHLBI's extramural investment, and a large proportion of its intramural investment addresses CVD. A major priority, as emphasized in the NHLBI Strategic Plan, is to enhance connections between basic and clinical studies through translational research, much of which relies upon the collaborative efforts of multidisciplinary investigative teams. The Cardiovascular Cell Therapy Network - a multicenter network of basic and clinical researchers in reparative medicine, interventional cardiology, statistics, and imaging technology - is investigating the therapeutic use of adult stem cells in patients with heart attacks and heart failure. The network is being renewed in FY 2012 and will collaborate with the Cardiothoracic Surgery Network to address end-stage heart failure patients who receive left-ventricular assist devices. A second translational program, the Progenitor Cell Biology Consortium, is supporting basic and preclinical studies of cell therapy for CVD. In FY 2012 NHLBI is renewing the Heart Failure Clinical Research Network and the Resuscitation Outcomes Consortium and launching the second phase of the Cardiac Translational Research Implementation Program, designed to move scientific discoveries into clinical practice.

During FY 2011, the *Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Health* (AIM-HIGH) trial was stopped ahead of schedule when it became apparent that the addition of niacin to standard statin therapy in high-risk patients with

heart disease offered no benefit. The *Claudication: Exercise Versus Endoluminal Revascularization* (CLEVER) trial, which evaluated the effectiveness of stenting versus supervised exercise in patients with blocked arteries in their legs, completed its active treatment phase. Two new trials are getting under way, *Cardiovascular Inflammation Reduction Trial* (CIRT), to test whether an anti-inflammatory drug prevents heart attack in high-risk patients, and *International Study of Comparative Health Effectiveness with Medical and Invasive Approaches* (ISCHEMIA) to evaluate aggressive versus conservative treatment strategies in patients with inadequate blood supply to the heart muscle because of coronary artery blockages. The Institute has made noteworthy progress in efficient design and management of such large, expensive trials.

NHLBI has a long tradition, dating from the 1948 establishment of the Framingham Heart Study, of supporting large cohort studies to understand CVD risk factors and suggest how heart attacks and strokes might be prevented. Many newer cohort studies focus on minority populations, including African Americans (the Jackson Heart Study and Coronary Artery Risk Development In Young Adults Study), Hispanics (the Hispanic Community Health Study), American Indians (the Strong Heart Study), and Alaska Natives (Genetics Of Coronary Artery Disease in Alaska Natives Study). The Multi-Ethnic Study of Atherosclerosis, which was designed to compare prevalence, correlates, and progression of early CVD among different ethnicities, includes a sizeable representation of Asian Americans.

Item

Chronic Obstructive Pulmonary Disease [COPD]. - The Committee applauds NHLBI's efforts to raise public awareness of COPD and encourages the Institute to work with community stakeholders and other Federal agencies, including CDC, to develop a national action plan to respond to the growing burden of this disease. (p. 88)

Action taken or to be taken

As the NIH component with primary responsibility for lung diseases, NHLBI supports extensive research and education activities on COPD. Its programs include basic science and animal studies of underlying disease mechanisms; clinical studies of COPD risk factors, genetics, molecular and cellular defects, disease progression, and co-morbidities; translational studies of pathways and drugs that may lead to better treatments; clinical trials, including comparative effectiveness research; and public and professional educational programs to increase awareness of COPD and knowledge about its symptoms, diagnosis, and treatment. Working with NCI, NHLBI is studying commonalities between COPD and lung cancer, both diseases in which smoking is a primary risk factor. This collaboration is leading to enrichment of the NCI/NHGRI Cancer Genome Atlas database with data pertinent to COPD. NHLBI cooperates with a number of other federal agencies on COPD. Examples are collaborations with CMS in the Long Term Oxygen Treatment Trial and with the FDA in SPIROMICS, a program to identify biomarkers for COPD and characterize the heterogeneity of the COPD population. VA medical centers participate in a number of NHLBI clinical trials for COPD. The CDC and several community stakeholders and patient representative organizations are partners in the NHLBI COPD Learn More Breathe Better national public health education campaign. NHLBI-CDC collaboration has also led to the introduction of a module on COPD in the Behavioral Risk Factor Surveillance

System Survey and to a recently released public health strategic framework for COPD prevention. Investigators supported jointly by NHLBI and AHRQ are setting up a large registry for comparative effectiveness research.

NHLBI concurs that development of a national action plan to respond to the growing burden of COPD could be beneficial. Toward that end, the Institute plans to host a forum of stakeholders and representatives from federal government agencies in FY 2012 to share information about current activities related to COPD and discuss opportunities for further cooperation and enhanced effectiveness of the federal response to this serious public health problem. The development of a federal action plan will be a topic of discussion at the forum.

Item

Jackson Heart Study. - The Committee recognizes that the Jackson Heart Study in Jackson, Mississippi, is the largest investigation of cardiovascular disease in the African American population. The Committee acknowledges the continued need for comprehensive research to address this health disparity and the important implications for such research to all persons threatened by cardiovascular disease. The Committee urges continued focus in addressing cardiovascular disease in African Americans at NHLBI and NIMHD. (p. 88)

Action taken or to be taken

The Jackson Heart Study (JHS) represents one of a number of NHLBI's longitudinal cohort studies that have substantial representation of African Americans. Others include the Coronary Artery Risk Development in Young Adults (CARDIA) study, with 50 percent African Americans; the Atherosclerosis Risk in Communities (ARIC) study, whose Jackson Field Center is exclusively African American; and the Multi-Ethnic Study of Atherosclerosis (MESA), with 28 percent African Americans and more than 60 percent minorities overall. These studies continue to reveal critical insights into the development of cardiovascular disease (CVD) in the community and to enable assessment of racial/ethnic differences in CVD risk factors, prevalence, and severity. Other NIH ICs – NIMHD and NIBIB – have funded components of JHS.

NHLBI also supports programs to investigate potential genetic determinants of CVD in African Americans and others. The Candidate gene Association Resource (CARE) contains genotype and phenotype data on 41,000 study participants pooled from nine NHLBI cohort studies, including genome-wide association study data on approximately 8,900 African American participants. The ongoing Women's Health Initiative (WHI) extension is following all African American and Hispanic participants for clinical events to improve power to test genetic associations with CVD outcomes. Genome-wide association and phenotype data are also available for 8,421 African American and 3,587 Hispanic women from WHI and 6,625 participants from MESA through NHLBI's SNP Health Association Resource (SHARe) project, a valuable and groundbreaking resource for research to identify genes underlying CVD.

Hypertension and its sequelae are highly prevalent among African Americans. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the benefits of four common medications in preventing CVD outcomes such as strokes; and follow-up of the trial participants for longer-term events is ongoing. The new

Systolic Blood Pressure Intervention Trial (SPRINT) will evaluate the benefits of maintaining systolic blood pressure at less than 120 mm Hg in adults at risk for heart disease or kidney disease; it is now recruiting at more than 80 clinical sites across the United States. As with ALLHAT, a substantial percentage of the SPRINT enrollees will be African American.

NHLBI spent 63.4% of its \$2.8 billion extramural budget in FY 2010 on CVD and has launched several research initiatives that will address other important aspects of CVD in African Americans. The Centers for Population Health and Health Disparities (CPHHD), located in five major cities, use what is known about the underlying causes of health disparities to develop effective interventions to improve the health of the affected population. The Baltimore, Chicago, and North Carolina centers involve more than 30,000 African Americans. Knowledge gained via NHLBI's extensive research portfolio on obesity, an important CVD risk factor that is widely prevalent in minority communities, will be of particular benefit to African Americans. An NHLBI Initiative titled Programs to Increase Diversity among Individuals Engaged in Health-Related Research (PRIDE) provides intensive mentorship and a research skills-enhancing experience to promote the scientific career development of faculty members and scientists from diverse backgrounds across a breadth of academic institutions. Several of the PRIDE Summer Institutes focus on CVD-related research.

Item

Marfan Syndrome and Thoracic Aortic Aneurysms. - The Committee commends NHLBI for its ongoing support of clinical research on Marfan syndrome in the pediatric population, and it encourages support for basic and translational research on this complex connective tissue disorder. The Committee also notes recent advancements in genetic research related to thoracic aortic aneurysms and encourages the Institute to promote additional research on this condition. (p. 88)

Action taken or to be taken

NHLBI continues its support for clinical, translational, and basic research related to Marfan syndrome in children and adults via investigator-initiated grants and special initiatives.

The Pediatric Heart Network (<http://www.pediatricheartnetwork.com>) has completed enrollment of 608 patients into a trial of therapy to slow progression of aortic root enlargement, a common and ominous manifestation of Marfan syndrome that can lead to aortic dissection or rupture. The study will determine whether the angiotensin II receptor blocker losartan is more effective than the beta-blocker atenolol (currently, standard therapy) in children and young adults with Marfan syndrome, and it will also compare side effects of the drugs. Patients are being followed for 3 years at more than 20 sites in North America and Europe. Several promising ancillary studies are examining genetic variations, treatment effects on strength and endurance and on bone and muscle mass, and quality of life in the participants. The National Marfan Foundation generously funds various aspects of the study.

NHLBI continues to support the Genetically Triggered Thoracic Aortic Aneurysms Registry (GenTAC) to advance the diagnosis and treatment of patients with genetically induced thoracic aortic aneurysms (TAAs). Although TAAs in older people are generally due to hypertension or

atherosclerosis, their appearance in young adults is more typically associated with rare genetic disorders such as Marfan syndrome. GenTAC collects medical data and biospecimens from affected individuals and makes them available to the scientific community for research, including genetic studies. To date over 2,700 patients have been enrolled, including almost 800 Marfan patients.

Item

Pulmonary Hypertension [PH]. - The Committee encourages NHLBI to support the establishment of a Pulmonary Hypertension Clinical Research Network to expand clinical trials and facilitate collaboration and data sharing among PH investigators. The Committee also continues to encourage the Institute to collaborate with the PH community to raise awareness of the disease. (p. 89)

Action taken or to be taken

NHLBI shares the interests of the Committee in supporting collaborative clinical research on Pulmonary Hypertension (PH). The Institute is working with the PH community through workshops and discussions to encourage investigators to respond to targeted clinical research initiatives and avail themselves of existing support mechanisms that foster clinical applications and new therapeutics development. In continuing to follow the NHLBI Strategic Plan for Lung Vascular Research, the Institute published the initiative “Pulmonary Vascular-Right Ventricular Axis Research Program” to support clinical research focused on the right ventricular failure that ultimately occurs in PH patients and causes their death. Investigators who are awarded support under this program will meet on an annual basis to discuss findings from their respective projects and identify common points for establishing future collaborative and/or consortium-based research efforts. To highlight knowledge gaps and identify obstacles to advancing consortium-based PH clinical research, NHLBI convened experts in adult and pediatric clinical research for the “Improving Outcomes in Pulmonary Vascular Disease” workshop. Participants identified the need for better phenotyping of clinical research subjects and design of better clinical end points for conducting future PH trials. Specific clinical research questions and interventions ready for testing were also delineated by workshop participants. These identified research needs can be addressed by existing NHLBI mechanisms such as “Phase II Clinical Trials of Novel Therapies for Lung Diseases” and “NHLBI Clinical Trials Pilot Studies.” Furthermore, an NHLBI program is being planned to catalyze development of candidate drugs and other products that will selectively support PH. Building experience with investigator-initiated PH clinical studies using these new programs should provide a strong foundation for future consideration of a PH clinical research network.

Because our portfolio of clinical trials in PH is very limited, NHLBI is not confident that establishment of a clinical research network would be the most productive approach at this time.

NHLBI also shares the Committee’s interest in collaborating with the community to raise awareness of the disease. Institute staff continues to collaborate with the Pulmonary Hypertension Association to provide up-to-date information on our activities at their annual meetings for dissemination by the association to its community of patients and physicians.

Item

RuSH Project. - The Committee supports the Registry and Surveillance System in Hemoglobinopathies [RuSH] project, which will determine the number of Americans with sickle cell disease, thalassemia and hemoglobin E disease. The Committee believes that NHLBI should retain control of the data system to fully characterize these patient populations and use the data to conduct research for new therapies, as well as to monitor the implementation of Healthy People 2020 using leading health indicators. NHLBI should also consult with HRSA concerning an expansion of sites for treatment centers. (p. 89)

Action taken or to be taken

The RuSH pilot is supported by an interagency agreement (IAA) between NHLBI and the CDC. Its planning phase began in 2009, and the implementation phase is funded from 2010 through 2012. Seven states - California, Florida, Georgia, Michigan, New York, North Carolina, and Pennsylvania - are receiving funding to send data that currently reside in their data systems to the CDC for analysis.

The CDC will use the state-specific data to generate statistically sound estimates of prevalence and population-level estimates of health care utilization and complication rates in the sickle cell disease and thalassemia patient populations. Because these data were collected for the purpose of surveillance, not research, consent is not required, and it is not possible to contact the patients represented in the state-specific data to obtain longitudinal information. Gathering patient-level data over time for research purposes will require a clinical data system (“registry”).

NHLBI will be responsible for a future clinical data system. Under terms of the IAA, the CDC will submit RuSH surveillance data and data system documentation to NHLBI. NHLBI will use these resources in combination with current projects to design and implement the clinical data system. The clinical data system will include hemoglobin E disease. Patient-level clinical data will be useful in planning new therapies and in monitoring Healthy People 2020 Objectives for hemoglobinopathies.

NHLBI and HRSA have embarked on a project to develop uniform medical language ontology for the hemoglobinopathies, which will enable federal agencies and researchers to use the same definitions and codes, thereby enhancing data comparability across different data systems and time periods. HRSA supports the Sickle Cell Disease Treatment Demonstration Program, the Thalassemia Treatment Demonstration Program, and the Sickle Cell Disease Newborn Screening Program. These activities will benefit from the ontology project by being able to standardize their datasets, ensuring comparability across sites, and report much-needed information about sickle cell and thalassemia patients to help support an expansion of the treatment centers.

Item

Sleep Disorders. - The Committee awaits the imminent release of the National Sleep Disorders Research Plan by the National Center on Sleep Disorders Research, which will articulate priorities and opportunities NIH-wide for addressing the challenge of sleep disorders and circadian disturbances. The Committee is concerned by the growing body of knowledge

demonstrating linkages between sleep disorders and a number of health conditions, including obesity, diabetes and cardiovascular disease, and the impact of sleep disturbances on safety at the workplace and in transportation. The Committee recommends more collaboration among ICs regarding sleep research and accelerated efforts in sleep research training. (p. 89)

Action taken or to be taken

The National Center on Sleep Disorders Research (NCSDR), a component of NHLBI, serves as the principal coordination point for NIH-wide sleep and circadian research. A major accomplishment in FY 2011 was the development of an updated NIH sleep research plan. Public health, medical, and research needs and priorities were assessed through several sources including a Request for Information, three public meetings of the Sleep Disorders Research Advisory Board, five external expert consultant panels, the Trans-NIH Sleep Research Coordinating Committee, and the input of institutes, centers, and offices NIH-wide. The process culminated in a sleep research plan endorsed by professional organizations, NIH, and DHHS. It was launched officially in November 2011.

NCSDR also coordinated new trans-NIH research programs in FY 2011. Acting on evidence that untreated sleep-disordered breathing contributes to the risk of maternal cardiovascular and metabolic disorders during pregnancy, NHLBI initiated a collaboration with NICHD to examine this relationship. A program announcement sponsored by NHLBI, NICHD, and NINR addresses basic understanding of the etiology and pathophysiology of sleep-disordered breathing in pregnancy. In addition to its focus on pregnancy-related issues, NICHD supports a wide range of research on the effects of sleep deprivation and disorders on human development, including studies of sudden infant death syndrome and of obesity in childhood and adolescence. A new Trans-NIH Obesity Research Plan highlights emerging opportunities to study the role of sleep in the development of obesity. An initiative jointly developed by NINDS and NIDDK is promoting the study of sleep and abnormalities in glucose regulation. NHLBI and NCI are collaborating on the collection of nationally representative data on sleep health in partnership with the CDC. NHLBI led an inter-agency and trans-NIH working group that used the data to establish the first national goals for sleep health in the DHHS Healthy People 2020 initiative. NHLBI and NICHD partnered on a new initiative for educational research to facilitate transfer of sleep-related information to health care providers, researchers, educators, and the public. Based on new findings implicating untreated sleep-disordered breathing in the genesis of disparities in cardiovascular health and quality of life, NCSDR convened a workshop to develop recommendations for enhancing existing disparities research programs and identifying new opportunities to develop interventions. NCSDR will continue to exercise a very active leadership role in coordinating and facilitating trans-NIH research, training, and education.

Item

Social Support. - NHLBI is encouraged to continue its research on how psychosocial factors, such as social support, may affect the course of prevention and treatment of, and recovery from, cardio-vascular illness or events. (p. 89)

Action taken or to be taken

NHLBI is pleased to support substantial research on the effects of psychosocial factors on cardiovascular disease (CVD) incidence and outcomes. Studies are examining the influence of social support provided within interpersonal relationships, families, neighborhoods, and broader social networks on CVD risk factors such as adverse diets, sedentary behavior, and obesity and on recovery and quality of life in patients who have heart attacks or heart failure.

NHLBI-supported projects on social support and cardiovascular health include:

- Studies to test the impact of enhanced family-provided support on (1) patient outcomes after placement of an implantable cardioverter defibrillator, (2) care quality and delivery for heart failure patients, or (3) re-hospitalizations following a heart attack.
- Examination of the role of social support within communities and neighborhoods in promoting healthy behaviors (e.g., wholesome diets and exercise) in children and adolescents, lowering the risk of metabolic syndrome in black families, or preventing development of visceral fat in perimenopausal women.
- Social networking studies using mobile phones and web-based technology to facilitate weight control and other health-promoting behaviors in young adults.

NHLBI is participating in several NIH-wide initiatives that address the influence of social networks and the social environment on health outcomes, including CVD outcomes. They include a program of basic research to expand application of social network methods and theory to improve health and, within the Basic Behavioral and Social Science Opportunity Network, an initiative that seeks to understand the mechanisms by which some social environments exert positive influences on health-related behavior.

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National Institute of Dental and Craniofacial Research (NIDCR)

Senate Significant Items

Item

Systemic Bone Active Therapeutics. - The Committee urges continued research on the effects of systemic bone active therapeutics on the craniofacial skeleton, including factors predisposing individuals to osteonecrosis of the jaw, as well as new approaches to facilitate bone regeneration. (p. 89)

Action taken or to be taken

NIDCR continues to support research in bone biology, diseases, repair and regeneration. Our 2009-2013 Strategic Plan articulates our commitment to research in this important area within the framework of Objective I-1: “integrate molecular, clinical, and population health approaches to improve diagnostics and optimize outcomes”, as well as Objective I-5: “facilitate reconstruction and regeneration of diseased or damaged oral and craniofacial tissues and organs through biological, bioengineering and biomaterials research approaches”.

Bone diseases afflict many Americans, with osteoporosis being the predominant health problem affecting eight million women and two million men. Another 34 million Americans suffer from osteopenia (low bone mass). Bone fractures due to osteoporosis are associated with increased mortality, morbidity, and economic burden. NIDCR supports basic bone biology studies to identify the molecular signals and pathways regulating bone formation and bone resorption. Information from these studies would shed light on basic mechanisms as well as therapeutic strategies for combating bone loss.

NIDCR also supports studies that seek to understand the potential side effects of systemic bone active therapeutics on the craniofacial skeleton. In particular, in the scientific literature, osteonecrosis of the jaw (ONJ) is reported in patients taking bisphosphonates by intravenous injections to treat bone pain from cancer metastasis. There are also rare reports of ONJ in patients taking oral bisphosphonates commonly prescribed to treat osteoporosis. ONJ is a painful non-healing exposed bone lesion in the upper or lower jaw. Often times, the condition develops following invasive dental procedures, such as tooth extraction, but ONJ can also show up spontaneously. Localized secondary infections are common, and overall, the condition is difficult to treat.

In 2011, a collaborative study conducted by the three NIDCR-supported regional dental practice-based research networks reported that risk for ONJ begins within two years of bisphosphonate treatment, for both cancer and non-cancer patients, and a higher risk was found in patients receiving the more potent form of the drug. Also in 2011, investigators supported by NIDCR discovered that one type of bisphosphonate specifically prevents bone healing by inhibiting the functions of bone remodeling cells, the osteoclasts, but allows for normal soft tissue healing. These results are bringing into focus the risk factors for the development and progression of this complicated disease. In fiscal year 2011, NIDCR reissued a funding opportunity announcement on “Pathophysiology and Clinical Studies of Osteonecrosis of the Jaw”. The goal is to stimulate additional research on the genetic, molecular and cellular basis of ONJ, novel approaches to

augment bone repair, and clinical studies on patient susceptibility and treatment options. New knowledge gained will further help develop prevention strategies for individuals who are currently taking or have been administered drugs that alter osteoclast function, as well as management and treatment options for ONJ patients.

Item

Temporomandibular Joint [TMJ] Disorders. - The Committee encourages NIDCR to collaborate with other ICs regarding the etiology and pathogenesis of TMJ disorders as well as the co-morbid chronic pain conditions and disorders that solely or predominantly affect women. In particular, NIDCR should work with NIAMS and NIBIB to develop research opportunities in the area of joint pain. Examples of topics that need more exploration include: a basic understanding of the kinematics and biomechanics of TMJ disorders as they relate to normal jaw function and in disease; the development of biomarkers in bone, muscle and cartilage that are predictive of temporomandibular disease progression; the interactions of the TMJ musculoskeletal system with the nervous system; and the development of non-invasive measures of TMJ bone structure, growth, degradation and repair. The recent scientific meeting of the TMJ Association, co-sponsored by NIDCR and other ICs, concluded that there needs to be a shift in research toward a systematic exploration of common underlying root causes. The Committee strongly urges NIH to heed the recommendations from this meeting, which have the potential to accelerate scientific progress not just in TMJ disorders but in the other coexisting conditions. (p. 89-90)

Action taken or to be taken

Temporomandibular Joint Disorders (TMJDs) are a complex set of disorders that cause recurrent or chronic pain and dysfunction in the jaw joint and its associated muscles and supporting tissues. NIDCR supports many projects related to TMJD and the common mechanisms underlying co-morbid chronic pain disorders including fibromyalgia, chronic fatigue syndrome, and vulvodynia. The NIDCR five-year Strategic Plan for 2009-2013 (<http://www.nidcr.nih.gov/Research/ResearchPriorities/StrategicPlan>) provides the framework for the future of TMJD basic, translational, and clinical research. The Institute's TMJD and Orofacial Pain Program articulate programmatic, health, and research goals for the next six years. This program aims to expand NIDCR's commitment to orofacial pain and genetics research and to position the TMJD research field to take advantage of genomic-era translational and clinical research opportunities to better prevent, treat, and diagnose TMJDs and other orofacial pain disorders. NIDCR also seeks opportunities to work across Institute boundaries to enhance research efforts on this debilitating disorder. In one example, NIDCR is working with NIAMS to conduct a careful analysis of the TMJ-associated pain measures included in the NIAMS-led Osteoarthritis Initiative, a multi-center, longitudinal, prospective observational study aiming to facilitate the scientific evaluation of biomarkers for disease onset and progression. NIDCR research efforts are also complemented by NIBIB studies in tissue engineering and repair of TMJ articular cartilage. In addition, NIDCR has supported a number of scientific workshops that focus on joint and other chronic pain conditions.

- NIDCR, NIAMS, and other NIH components co-funded a meeting in December 2010 on Pain and Musculoskeletal Disorders: Translating Scientific Advances into Practice. At

the conference, investigators from different disciplines discussed topics that included the role of neural factors in an individual's pain sensitivity, and how the latest research techniques in the pain field can be applied to joint disorder studies.

- NIDCR worked with the NIH Office of Research on Women's Health, and the Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Working Group on a State of the Knowledge Workshop on ME/CFS, held in April 2011, that evaluated the current knowledge of ME/CFS, identified gaps in the research, and sought out opportunities where science and technology can accelerate research progress and improve medical care for people with this illness.
- In June 2011, NIDCR sponsored the 6th TMJ Association Scientific Meeting "Comorbid Chronic Pain Conditions: Mechanisms, Diagnosis and Treatments". The meeting was co-sponsored by several other NIH Institutes, and participants included seven NIH Institute, Office, and Center Directors and the leaders of four patient advocacy groups composing the Chronic Pain Research Alliance.
- NIDCR also participated in the Eunice Kennedy Shriver National Institute of Child Health and Human Development workshop "Vulvodynia: A Chronic Pain Condition - Setting a Research Agenda" in July 2011. Investigators discussed the biological processes that lead to vulvodynia and the best approaches for stimulating the most promising research on vulvodynia and related pain syndromes.

NIDCR, NINDS, and 10 other NIH Institutes are developing an NIH-wide workshop on chronic overlapping pain conditions to be held in 2012. A working group has been formed and will be meeting during the next several months to refine the agenda for this upcoming workshop. This working group is comprised of program officers who manage research portfolios containing the various potentially overlapping chronic pain conditions. Their charge includes working together over time to examine their individual portfolios to identify research gaps and opportunities for collaboration that might accelerate research into the common mechanisms underlying many of these conditions.

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National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Senate Significant Items

Item

Chronic Pelvic Pain. - The Committee is pleased by the progress made in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain [MAPP] Research Network, particularly the inclusion of male subjects, as the research plan continues to focus on the natural history of interstitial cystitis. The Committee encourages the MAPP Research Network to collaborate closely with patient health organizations. (p. 90)

Action taken or to be taken

The MAPP Research Network is continuing studies that will better define the two most common urologic chronic pelvic pain conditions, interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The Network's collaborative Trans-MAPP Epidemiology and Phenotyping Study aims to elucidate the natural history of these conditions and to determine if there are unique patient subgroups that behave differently, and thus might benefit from different treatment approaches.

Recruitment of urologic chronic pelvic pain patients in the multi-site MAPP Research Network is proceeding across all participating sites and is currently on pace to be completed in 2012. Recruitment of male urologic chronic pelvic pain patients, including men with IC/PBS, has continued to improve over the last 12 months. The study remains committed to meeting the recruitment goals for male patients and to a better understanding of IC/PBS and CP/CPPS in men. Recruitment of healthy controls and other comparison groups is proceeding as well.

Already, new information about symptom "flares" in IC/PBS is emerging from the MAPP Research Network studies, including characteristics of flare patterns over time. This information will be important to the design of future clinical trials.

In addition to the natural history study, the Network is pursuing other studies - including imaging studies of brain structure and function, studies to identify biomarkers of disease, and efforts to assess the possible role of infectious agents - that are part of the Network's integrative multi-disciplinary approach to understand how and why urologic chronic pelvic pain conditions develop.

The success of the MAPP Research Network's efforts thus far has been helped by the Institute's collaborations with patient health advocacy organizations, including the Interstitial Cystitis Association and the Prostatitis Foundation. For example, patient advocacy organizations have publicized the MAPP study on their Web site to help bolster recruitment, and have provided feedback on the Network's activities through attendance at Steering Committee meetings and through other avenues of communication. Because the possible pathological relationships between urologic chronic pelvic pain and pain conditions often found in the same patients - irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia - are another key research focus of the Network, NIDDK is also reaching out to other health advocacy groups focused on pain to obtain additional expertise that could enhance the MAPP Research Network's success.

Item

Depression and Diabetes. - NIDDK is encouraged to strengthen collaborations with other institutes regarding research on the links between diabetes and depression. (p. 90)

Action taken or to be taken

Recently, several major studies jointly supported by multiple components of NIH have provided significant new insights about the bi-directional relationship between diabetes and depression. The Nurses' Health Study examined the link between the diseases in over 75,000 women. The large size of study allowed the investigators to measure the increased incidence of diabetes with depression and of depression in women with diabetes, and to examine how treatment of one condition affected rates of the other. The researchers also found that women with both diabetes and depression had double the mortality of women with neither condition.

The NIDDK-led Look AHEAD study, which is examining lifestyle change in people with type 2 diabetes, reported that participants with depression had more risk factors for cardiovascular disease. The NIDDK-led Diabetes Prevention Program (DPP) and the DPP Outcomes Studies, which showed that people with pre-diabetes can dramatically reduce their risk of developing type 2 diabetes through lifestyle changes that achieve modest weight loss, have also studied the relationship between diabetes and depression, reporting increased diabetes risk in those on antidepressant medications. This research, and findings from other studies jointly supported by multiple NIH Institutes and Centers, clearly highlights the link between diabetes and depression, and the need to develop integrated treatment approaches that address both conditions at the same time in a way that can be realistically implemented through primary care. Accordingly, NIDDK is working with NIMH to hold a conference in 2012 on the relationship of diabetes and depression. The agenda will focus on both the bi-directional biological impact of the diseases on one another, and on improved approaches to prevention and treatment.

NIDDK and NIMH co-funded a landmark study to improve care for patients with both depression and diabetes. The researchers examined a primary care approach called "TEAMCare," in which nurses worked with patients and their physicians to manage care for depression and poorly controlled diabetes in an integrated fashion, using evidence-based care guidelines. With this approach, patients experienced less depression, better control of blood sugar, improved quality of life, and higher satisfaction with care, as compared to patients receiving usual care.

NIDDK and NIMH also jointly issued a program announcement to encourage research to increase understanding of metabolic syndrome in persons with serious mental illnesses. The announcement, entitled "Adverse Metabolic Side Effects of Second Generation Psychotropic Medications Leading to Obesity and Increased Diabetes Risk," resulted in funding of several large-scale studies.

In 2010, NIMH and NIDDK, together with other NIH Institutes, convened a workgroup focused on improving care for patients with co-occurring medical conditions, especially depression and diabetes, in primary care settings. The workgroup is in the process of developing a funding

opportunity announcement to further encourage research on practical approaches for integrating and improving care for patients with co-occurring disorders.

Item

Diabetes Prevention Program. - The Committee recognizes the success of the NIDDK funded Diabetes Prevention Program, a clinical research trial which found that modest weight loss through dietary changes and increased physical activity could prevent or delay the onset of type 2 diabetes significantly. The Committee urges NIDDK to support further diabetes research that will build upon past successes, improve prevention and treatment, and close in on a cure. (p. 90)

Action taken or to be taken

Building on the dramatic results of the Diabetes Prevention Program (DPP) has been and will continue to be a key programmatic priority of NIDDK. The Institute continues to follow the DPP cohort through the DPP Outcomes Study, which found that the interventions remain effective for at least 10 years. This work has included notable translational research designed to lower the cost and maintain the efficacy of the DPP lifestyle intervention, which is particularly effective at reducing the incidence of type 2 diabetes. Separate research studies funded through this effort have tested group delivery of the intervention by YMCA employees or by community health workers, among other approaches. Initial results in the YMCA study were sufficiently encouraging to lead to implementation of the National Diabetes Prevention Program, led by the CDC, to train and certify lifestyle coaches to deliver the group intervention and make this life-saving health care strategy both affordable for and available to the millions of Americans who may benefit from it.

Item

Functional Gastrointestinal Disorders and Gulf War Syndrome. - The Committee recognizes the direct link between functional gastrointestinal disorders, such as irritable bowel syndrome and functional dyspepsia, and gulf war syndrome, as detailed in the Institute of Medicine report "Gulf War and Health: Volume 8. Health Effects of Serving in the Gulf War." The Committee urges NIDDK to collaborate with the Department of Defense and the Department of Veterans Affairs to advance research on the etiology, natural history and quality of functional gastrointestinal disorders in patients with gulf war syndrome. (p. 90)

Action taken or to be taken

NIDDK supports a strong portfolio of research projects aimed at understanding and improving treatment of functional gastrointestinal disorders, such as irritable bowel syndrome (IBS) and functional dyspepsia. The NIDDK's basic research portfolio in this area includes studies of the etiology and the natural history of each of these disorders. Recent research on IBS has shown that patients with the disorder perceive visceral pain associated with IBS differently than healthy volunteers, and exhibit altered brain activity responses to both pain and anticipation of pain. In addition, pain responses are heightened in IBS patients who have experienced physical abuse. This research on IBS-related pain may lead to improved treatment strategies and outcomes.

Additionally, the Institute supports clinical research on ways to improve treatment outcomes and quality of life. For example, a new clinical trial is testing a self-administered behavioral treatment program called cognitive behavioral therapy as an effective, accessible, and affordable form of IBS therapy. The results of this study may be of benefit to veterans, including veterans with Gulf War Syndrome, with this and other forms of functional gastrointestinal disorders. NIDDK is also considering ways to reach out to the Department of Veterans Affairs and the Department of Defense to explore potential collaborations on advancing research in this area.

Item

Gestational Diabetes. - The Committee urges NIDDK to explore additional opportunities for research on gestational diabetes, particularly regarding possible long-term health consequences such as a susceptibility to type 2 diabetes. (p. 90)

Action taken or to be taken

NIDDK is pursuing numerous research opportunities and other efforts to better understand gestational diabetes (GDM) and reduce its health impact on women and their families. Maternal obesity and excess gestational weight gain have been shown to be important risk factors for the development of GDM, postpartum weight retention, and metabolic disease later in life - including greater risk of future type 2 diabetes in both mother and child. The NIDDK, NICHD, NHLBI, NCCAM, the NIH Office of Research on Women's Health (ORWH), and the NIH Office of Behavioral and Social Sciences Research (OBSSR) recently partnered on an initiative to support clinical trials of short-term lifestyle interventions in overweight and obese pregnant women, funding several studies in FY 2011. Interventions that are successful in reducing excessive maternal weight gain, improving glycemia (the control of blood sugar) and other metabolic parameters in the mother, and preventing large for gestational age infants and neonatal metabolism problems could have far-reaching effects on the later development of diabetes, obesity, and other health problems among women and their children. In another effort, the National Diabetes Education Program (NDEP), a partnership of the NIH/NIDDK and the CDC, used American Reinvestment and Recovery Act funds to award a contract for the development and testing of evidence-informed, innovative interventions designed to increase the adoption of prevention interventions for women with a history of GDM - a population at significantly increased risk of developing type 2 diabetes. The interventions will seek to improve postpartum diabetes testing rates and increase adoption of behaviors identified in the Diabetes Prevention Program (DPP) clinical trial that will reduce or delay the development of diabetes among these women. This effort is in its second year. At the same time, the DPP itself has continued to follow up on the participants with a history of GDM to learn more about how the DPP interventions affected their long-term risk of developing type 2 diabetes, versus trial participants without this unique risk factor. An analysis of the 10-year follow-up is forthcoming. In addition to human studies aimed at developing strategies to reduce the onset and impact of GDM, NIDDK supports basic research studies in animal models to understand mechanisms whereby GDM develops - research that may benefit both women at risk for GDM and people at risk for type 2 diabetes. Finally, the NDEP, in partnership with the NIH ORWH, continues to pursue a robust awareness and outreach campaign for women with a history of GDM, their families, and health care providers. Using multiple print and electronic media outlets, targeting "special events" such as Mother's Day and Women's Health Week, and building partnerships with groups such as the

Healthy Mothers, Healthy Babies Coalition, the campaign has sought to amplify and extend the reach of critical post partum messages regarding the lifelong risks to both mother and child that are associated with a history of GDM.

NICHD agrees that the impact of GDM extends beyond the pregnancy itself, and recently, the role of GDM in long-term adverse health outcomes in the offspring of affected mothers has gained more attention. NICHD is planning a Consensus Development Conference in late 2012 with the NIH Office of Medical Applications of Research, entitled “Diagnosing Gestational Diabetes Mellitus.” Over the last decade, NICHD-funded studies have shown that treatment of mild GDM improves pregnancy outcomes and that the risks of adverse outcomes increase across the spectrum of maternal glycemia during pregnancy. However, these research results have not been adequately translated into practice, and opinions still differ on the value of universal screening for GDM and what should be the thresholds for the diagnosis of GDM. This conference will allow a rigorous evaluation of existing evidence and develop a statement that advances understanding of the issue that will be useful to health professionals and the public.

Item

Glomerular Diseases. - The Committee recognizes the recent progress made in understanding glomerular diseases, such as focal segmental glomerulosclerosis [FSGS], including the discovery of specific genetic factors which make African Americans five times more likely to develop FSGS than Caucasians. The Committee urges NIDDK to continue to support research on glomerular diseases and collaborate with NIMHD to expand research on the impact these diseases have on minority populations. (p. 91)

Action taken or to be taken

Due in part to NIDDK-supported research, scientific advances in the area of glomerular disease - such as minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN) - are accelerating on multiple fronts, including genetics, clinical research, podocyte biology, and discovery science. Over the past 10 years, mutations in nearly 20 different genes associated with kidney function have been linked with FSGS. The identification of two specific variations in the *APOL1* gene that are associated with much of the increased risk of FSGS and other non-diabetic forms of kidney disease in African Americans may yield important insights into the causes of disease and possible treatments. Two circulating factors have recently been implicated in recurrent FSGS, and a third in MN. These factors provide and represent important advances in understanding the causes and possible treatments for this form of glomerular disease, and suggest many additional therapeutic targets that can be engaged with less toxic therapies. In the future, scientists and physicians can use this combination of genetic information and circulating factors to study mechanism of disease, improve diagnosis and risk prediction, aid treatment decisions, determine drug dosage, and choose between multiple drug targets in designing research studies and patient therapies.

Currently, NIDDK has one active program announcement for investigator-initiated research projects related to glomerular diseases, issued in February 2010. Research relevant to this announcement includes studies designed to address a number of different aspects concerning the pathogenesis, natural history, therapy, pre-emption, or prevention of the various forms of

glomerular disease. Thus far, five applications received in response to this announcement have been funded. In addition, NIMHD has issued a solicitation to encourage research on health disparities, and one specific area of research emphasis is FSGS. NIDDK is also planning a meeting for April 2012, entitled “Reducing the Impact of Glomerular Disease: Pathophysiology, Diagnosis, Therapy, and Clinical Trial Design.” Participants will address the mechanisms of deranged immunity that affect FSGS and other glomerular diseases; reliable tests for early diagnosis; old and new therapies for these diseases; design of therapeutic trials; and mechanisms for pathways of cooperation among industry, academia, government, and patient advocacy groups.

The Nephrotic Syndrome Study (NEPTUNE) is an integrated group of academic medical centers, patient support organizations, and clinical research resources dedicated to advancing the understanding and treatment of MCD, FSGS, and MN that is supported by the NIH Office of Rare Disease Research and NIDDK. Approximately 150 patients are now enrolled in this trial, and over one thousand have joined the patient registry. This consortium of research groups receives significant support from The NephCure Foundation and the Halpin Foundation. NIDDK, NIMHD, and other NIH components continue to build on this and other collaborations to better understand and address the high prevalence of FSGS in African Americans.

Item

Inflammatory Bowel Disease [IBD]. - The Committee commends NIDDK for recent advancements in IBD research and encourages continued support for the study of genetic, cellular and environ-mental factors that contribute to the development of these complex diseases. The Committee also notes the increasing incidence of IBD in children and urges the Institute to expand support for genetic and clinical studies of pediatric patients. (p. 91)

Action taken or to be taken

NIDDK continues to support a significant inflammatory bowel disease (IBD) portfolio that includes research investigating the genetic, cellular, and environmental factors that contribute to the development of this disease. A key element of the Institute’s IBD research portfolio is the NIDDK Inflammatory Bowel Disease Genetics Consortium (<http://medicine.yale.edu/intmed/ibdgc/index.aspx>), which is an international leader in identifying, sequencing, and characterizing the genetic variants that contribute to the risk of IBD. The numerous genetic factors identified thus far that contribute to IBD risk have varying degrees of impact, ranging from strong to subtle. Recently, the Consortium supported two international studies designed to enhance identification of risk variants which make subtle, yet significant, contributions to disease. Both studies performed meta-analyses of data collected from multiple studies, which provides a greater statistical advantage. In the first study, researchers performed a meta-analysis of the combined data from six genome-wide association studies to search for variants associated with ulcerative colitis. This meta-analysis yielded 29 novel variants, bringing the total number of known variants associated with ulcerative colitis to 47. The researchers used various analytical tools to determine which genetic variants, that were located within newly-identified chromosomal risk locations (loci), were likely to confer disease susceptibility. Further analysis found that many of these variants are linked to biological pathways that contribute to IBD. In the second study, researchers used meta-analysis to search for genetic variants associated

with Crohn's disease. With this approach, the research team identified 30 novel variants, bringing the total number of known variants associated with Crohn's disease to 71.

NIDDK has expanded its pediatric IBD portfolio with the funding of a new planning grant for a pediatric colitis clinical study, "Predicting Response To Standardized Pediatric Colitis Therapy: The PROTECT Study." Although the degree of severity of ulcerative colitis symptoms greatly vary and require treatments with a wide range of toxicities, there are no guidelines for clinicians treating these children. This clinical study, for which support is pending peer review of the final proposal, would treat over 400 children who have been newly-diagnosed with ulcerative colitis with optimal care that is responsive to disease severity. The children would be followed closely for a 2 year period and the impact of clinical, genetic, environmental, and immune factors on disease progression or remission will be analyzed. The goal of this study is to utilize treatment analysis data to develop a model correlating clinical, genetic, and immunologic information to aid clinicians in formulating individualized treatment plans for their pediatric patients that will achieve clinical remission of colitis with minimal exposure to toxic medications or the need of surgery. The results of this study would also be integrated with an on-going pediatric Crohn's disease study sponsored by the Crohn's and Colitis Foundation of America.

Item

Pediatric Functional Gastrointestinal Disorders [FGIDs]. - The Committee urges NIDDK to work with NICHD to support research on the quality of life for children suffering from FGIDs, which often interfere with emotional, social and professional development and can impair physical, economic and educational well being. (p. 91)

Action taken or to be taken

With a shared interest in improving the quality of life for children who suffer from functional gastrointestinal disorders (FGIDs), NIDDK and NICHD collaborate closely, although most investigator-initiated grant applications are assigned to NIDDK, with NICHD serving in an ancillary funding role. NIDDK supports a study of the collective microbial genes (microbiome) present in the intestines of children with FGIDs, such as irritable bowel syndrome and constipation, compared to healthy children. Through sequencing the genomes of microbes living in the intestines of these children, this research will improve understanding of the composition of intestinal microbes in children with and without these disorders. This knowledge will enable investigations into whether unique differences in the intestinal microbiome contribute to FGIDs in children, and how the intestinal microbial community might be modified to improve health outcomes and quality of life for children with these disorders.

NICHD is supporting research to understand the biopsychosocial processes associated with pediatric chronic abdominal pain lacking a specific medical diagnosis. Children with such pain are thought to be at increased risk for FGIDs, headache and other chronic pain disorders, and psychiatric disorders as adolescents and adults. The study will identify characteristics of youth with chronic abdominal pain who are most likely to experience chronic pain and psychiatric disorders as adolescents and young adults, and it will suggest factors that should be addressed in prevention and treatment efforts.

In addition, another NICHD-supported study planned for the coming year will test an intervention in which parents are trained to address functional abdominal pain in their children. Study investigators will collect data on the children's symptoms, functional disability, health care utilization, quality of life, parental responses to children's illness behavior, and children's ability to cope with pain. If successful, this intervention could provide a useful model for the development of other effective, accessible interventions for FGIDs and similar medical problems.

Item

Pediatric Kidney Disease. - The Committee supports NIDDK's research emphasis on pediatric kidney disease and continues to encourage the development of multicenter, pediatric prospective clinical/translational trials. (p. 91)

Action taken or to be taken

NIDDK has taken several actions to address the important problem of kidney disease in children and adolescents. The Chronic Kidney Disease in Children (CKiD) study has had 15 scientific publications in the past year informing the community about newly defined risk factors for disease, as well as early manifestations of disease. The Institute has expanded investment in the two ongoing studies of pediatric kidney disease. An ancillary study to CKiD was funded to investigate genetic factors associated with progression of kidney disease in this population, and compare with a European cohort. The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial is comparing prophylactic antibiotic treatment with placebo for prevention of urinary tract infections and kidney scarring in children with reflux. Patient recruitment was completed in May 2011, and follow-up ends May 2013. Two ancillary studies to the trial have been funded - one looking at genetic predisposition to infection and another looking at urinary tract infection in children without reflux.

The NIDDK-supported Focal Segmental Glomerulosclerosis (FSGS) Clinical Trial was designed to compare two different approaches to treating steroid-resistant FSGS in children and young adults. After 1 year, the difference in response rates between the two groups was not statistically significant, underscoring the importance of continued research to identify new markers of disease progression (biomarkers) and factors that contribute to this disease which may provide new targets for therapy. NIDDK, along with NIH Office of Rare Diseases Research and two patient advocacy groups, supports the Nephrotic Syndrome Rare Disease Clinical Research Network (NEPTUNE). It is a multi-site, multidisciplinary collaborative research and education network designed to foster innovative approaches to the understanding of three glomerular diseases: minimal change disease, FSGS, and membranous nephropathy.

NIDDK is also concerned about kidney stone disease in pediatric patients. The Institute has funded the Rare Kidney Stone Consortium to study four diseases characterized by deposition of crystals in the kidneys that often lead to kidney stones and kidney failure. It focuses on the discovery of biomarkers of disease risk, disease activity, and response to therapy.

Finally, the Institute is conducting a "Kidney Research National Dialogue," an effort to strategically plan its future research focus for kidney disease, including pediatric kidney disease.

The Dialogue is intended to strengthen the NIDDK's kidney research programs by developing a "Blueprint for Kidney Disease Research," to inform future NIDDK kidney disease research planning and program management.

Item

Polycystic Kidney Disease [PKD]. - The Committee urges NIDDK to collaborate with other institutes and leverage discoveries from its portfolio of PKD grants for the purpose of developing a comprehensive strategic plan for PKD and other related neo-plastic genetic diseases. For example, the Committee understands that cysts in PKD emulate the uncontrolled cell growth observed in cancer. The Committee believes this analysis will allow NIH to more effectively use Federal funds, create and identify additional public-private partnerships to maximize investments, and more quickly move PKD research findings to clinical trials. (p. 91)

Action taken or to be taken

NIDDK is conducting a "Kidney Research National Dialogue," an effort to strategically plan its future research focus for kidney disease, including PKD. This effort is designed to strengthen both the Institute's kidney research programs as well as the broader nephrology research community. Development of a "Blueprint for Kidney Disease Research" will inform future NIDDK kidney disease research planning and program management and identify key areas of research opportunity for the community.

Previous studies have indicated that slow, constrained cyst growth results from changes in cellular architecture, fluid secretion, and non-cancerous cell proliferation. NIDDK continues to support studies focused on determining the mechanisms that drive cyst growth and therapies that slow or prevent this process.

With regard to ongoing PKD research, two large NIDDK-funded clinical studies - HALT-PKD and CRISP - are focused on identifying better monitoring and imaging approaches as well as improvements in patient care for individuals with the most common form of PKD. The Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to develop innovative imaging techniques and analyses to follow disease progression or to evaluate treatments. The image analysis methods developed in CRISP are currently being implemented in HALT-PKD and have been used by industry-sponsored trials for patients with PKD. The HALT-PKD study has been extended to test the blockade of the renin-angiotensin system as a therapy for PKD and to demonstrate the validity of total kidney volume and other biomarkers as surrogates for progression of disease. NIDDK has also published a research solicitation to encourage applications from the current CRISP investigators that would allow them to continue following this well-characterized and highly motivated patient group and to provide a platform for informative ancillary studies. NIDDK has funded further genetic research to identify genes that determine the severity of the disease.

Four PKD Research and Translational Centers perform basic and clinical research to develop and test additional promising therapies. The purpose of the Centers is to provide resources for communication and collaboration between basic and clinical researchers in the field of PKD. The shared resources will enhance the efficiency of research and foster collaborations with

and among institutions with strong existing PKD research programs. For example, the development and study of new animal models is leading to studies that will likely translate to human mechanisms and new therapies.

NIDDK has supported extensive and ongoing data collection related to volumetric analysis of kidney images, PKD genotyping, and surrogate marker analysis in the HALT-PKD and CRISP studies. These data and samples are available to the research community through the NIDDK Repository and are currently being used by outside investigators. In addition to these efforts, an NIDDK initiative is encouraging identification and validation of biomarkers and risk assessment tools for kidney function, injury, and disease progression in people with chronic kidney disease. Improved biomarkers for screening, monitoring kidney function, and managing chronic kidney disease would be of benefit to people with PKD.

Item

Vitamin D Deficiency and Chronic Kidney Disease. - The Committee is pleased to note the full range of bone and mineral research under way in both the intramural and extramural programs at NIDDK, including the additional research emphasis the Institute is placing on the relationship between vitamin D deficiency and chronic kidney disease. These research findings are expected to be particularly relevant to national efforts aimed at reducing health disparities in diverse populations. (p. 91)

Action taken or to be taken

NIDDK recognizes the importance of Vitamin D to the morbidity and mortality of patients with chronic kidney disease (CKD). The Institute currently supports research investigating the role of vitamin D in chronic renal insufficiency. In addition, an NIDDK-supported randomized ancillary clinical trial is assessing whether vitamin D supplementation can prevent the development and progression of diabetic kidney disease. With respect to conditions which predispose people to forming defective bone tissue, NIDDK supports research to develop noninvasive detection methods to monitor bone health. The Institute continues to fund studies to understand the mechanisms of vascular calcification in the setting of CKD. Specifically, the Chronic Renal Insufficiency Cohort (CRIC) Study is examining coronary artery calcification prospectively in patients with chronic kidney disease. NIDDK recognizes the increased risk of cardiovascular disease in patients with end-stage renal disease and supports research studies to address this important issue.

In addition to these efforts, in 2011, NIDDK-supported scientists identified a new biomarker that may be an important predictor of progressive kidney failure and death. In a study published in the *Journal of the American Medical Association*, researchers reported that high levels of a hormone (FGF-23) that regulates phosphate metabolism are associated with an increased risk of kidney failure and death among people with CKD. (Phosphorus is used to build and repair bones and teeth, to help cells function, and to maintain DNA. The kidneys help control the amount of phosphate - which consists of one phosphorus atom bound to several oxygen atoms - in the blood by eliminating excess. Elevated phosphate levels are often a consequence of kidney damage or advanced kidney disease.) Measuring the levels of FGF-23 in patients with CKD could help to identify those whose kidney function is likely to be stable over time as compared to those whose

disease is likely to progress and who may require more intensive therapy. In a study published in the *Journal of Clinical Investigation*, this group showed that blocking FGF-23 in a rat model of CKD either genetically or with an antibody reduced cardiac fibrosis, a possible contributor to cardiac dysfunction seen in patients with CKD or on dialysis. Future studies will determine whether elevated FGF-23 plays an active role in the deterioration of kidney and/or cardiac function in CKD patients or is simply an indicator of poor prognosis, and whether reducing levels of this hormone improves patient prognosis and survival.

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National Institute of Neurological Disorders and Stroke (NINDS)

Senate Significant Items

Item

Dystonia. - The Committee commends the participation of NINDS in the Dystonia Coalition and encourages continued investments in dystonia research. (p. 91)

Action taken or to be taken

The dystonias are movement disorders in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures. The movements, which are involuntary and sometimes painful, may affect a single muscle; a group of muscles such as those in the arms, legs, or neck; or the entire body. NINDS continues to support the Dystonia Coalition, working closely with the NIH Office of Rare Disease Research (ORDR) which leads the Rare Diseases Clinical Research Network of which the Coalition is a member. The Coalition is a collaboration of medical researchers and patient advocacy groups that is advancing the pace of preclinical and clinical research to find better treatments and a cure. Because of the extraordinary enthusiasm among the scientific and lay dystonia community, the Coalition has expanded to include 44 clinical sites and 13 patient advocacy groups, with several pharmaceutical companies also engaged through participation at the Coalition's annual meeting. Information about the Coalition's activities is widely disseminated through scientific meetings and other outreach efforts, including the website (<http://rarediseasesnetwork.epi.usf.edu/dystonia/>). The Coalition has overcome the organizational challenges that are inherent to such a broad cooperative effort, fulfilled the regulatory requirements for the initial clinical studies, ensured consistency and sharing of data across clinical sites, and begun clinical studies with dystonia patients. Initial clinical studies are focusing on the natural history of dystonias, the collection of biorepository specimens for the use of dystonia researchers via the NINDS Human Genetics Repository, and the development of rating scales that can be used to diagnose different forms of dystonia and monitor their severity over time. Six pilot studies have also been selected in keeping with the Coalition's aim to rapidly select and fund promising early clinical studies, and one has already progressed to obtain an NIH R01 grant to continue the project. The Coalition is also taking steps to encourage junior investigators and senior investigators not previously studying dystonia to move into research on this disease.

NIH also continues to invest in a wide range of dystonia research that complements the efforts of the Coalition. For example, new and ongoing grants, for example, focus on understanding how gene mutations cause dystonia, developing better mouse models of the disease, screening for drugs based on targets gleaned from previous genetic studies, and understanding and improving deep brain stimulation therapy. NINDS has also funded small business grants as part of a collaboration with the FDA to improve testing of botulinum toxin. Botulinum toxin is an effective therapy for many people with focal dystonias (dystonias that are limited to a single area of the body), but variability in the potency of toxin produced by different manufacturers has been a problem. Standardization of potency is important to prevent over- or underdosing of patients.

Item

Epilepsy. - The Committee applauds the establishment of the Interagency Collaborative to Advance Research in Epilepsy [ICARE], led by NINDS, which includes all Federal institutes and centers that fund epilepsy research along with voluntary organizations in the field. The Committee encourages ICARE's continuation as a venue for sharing efforts and perspectives on finding cures for epilepsy. The Committee also commends NINDS for its plans to create the Epilepsy Centers Without Walls program, which will promote multidisciplinary research efforts targeted toward specific topic areas in epilepsy, including epileptogenesis, comorbidities and mortality in epilepsy. (p. 92)

Action taken or to be taken

NINDS hosted the second annual meeting of the Interagency Collaborative to Advance Research in Epilepsy (ICARE) on June 27, 2011. ICARE representatives serve as points of contact for facilitating communication and collaboration across organizations that support epilepsy research. The meeting was an opportunity for member groups to share information about their epilepsy research activities, and to discuss priorities and challenges for future research. The meeting's afternoon session focused on Sudden Unexpected Death in Epilepsy (SUDEP), with an overview of SUDEP research and a discussion of goals and progress in the context of efforts supported by ICARE members. NINDS will continue to lead and partner with ICARE members, through annual meetings and other collaborative activities. In particular, ICARE members will be invited to participate in the next Curing Epilepsy conference, to be held in 2013. These conferences, originally initiated by the White House and previously sponsored by NINDS in 2000 and 2007, bring together scientists, clinicians, and patient and professional organizations to discuss priorities for epilepsy research. As outcomes, participants have developed and updated the Epilepsy Research Benchmarks, a set of research goals shared by the entire epilepsy community. The third Curing Epilepsy conference will review the state of epilepsy research today, assess progress made since 2007, and develop a new set of Benchmarks to guide future advances.

In 2010 and 2011, NINDS announced several new initiatives for epilepsy research. One of these, the Epilepsy Centers without Walls program, supports multidisciplinary consortia to solve specific challenges in the prevention, diagnosis, or treatment of the epilepsies and associated comorbidities. The first of a series of funding opportunity announcements (FOAs) for this program focused on human epilepsy genetics. Although causal genes have been identified for a number of rare, familial epilepsy syndromes, the genetic contributors to more common forms of epilepsy are not well known. The awarded Center, called the Epi4K project, aims to identify new genes and genetic pathways by analyzing 4000 genomes of epilepsy patients and families collected by several major research groups. NINDS is also supporting planning grants in advance of future Centers without Walls for other aspects of epilepsy. Two projects will work toward a Center focused on SUDEP: one will develop a clinical data acquisition, management, and integration system for identifying SUDEP cases and physiological risk factors, and the other will begin a multisite collaboration combining basic science, human genetics, and clinical physiology to search for additional risk factors. NINDS has released a new FOA for planning support toward a Center focused on treatments to prevent epilepsy or modify the course of disease.

For approximately one-third of people with epilepsy, seizures are not adequately controlled by available treatments. Another new NINDS initiative supports translational research to develop

new ways to treat epilepsy or prevent epileptogenesis, the process through which brain tissue develops a propensity for spontaneous recurring seizures. NINDS has recently funded a project through this program to develop a seizure prediction and drug delivery system that will administer antiepileptic drugs only at times of high seizure likelihood. Such intelligent drug delivery may not only prevent seizures, but it should also limit adverse cognitive and physical side effects associated with chronic antiepileptic drug exposure. The remaining new NINDS initiative for epilepsy research, the Epilepsy EUREKA program, encourages innovative and transformative studies to uncover disease mechanisms and identify new treatment or preventive strategies. NINDS has made four awards through this program, each of which employs the latest research methods to provide new insights into understanding and ultimately treating epilepsy.

Item

Muscular Dystrophy. - The Committee commends NIH for collaborating with the Parent Project Muscular Dystrophy [PPMD] End Duchenne Grant Award Program by referring applicants who propose translational research on Duchenne muscular dystrophy but miss NIH paylines to PPMD for the opportunity to seek bridge funding. The Committee encourages additional efforts at NIH to translate research findings on Duchenne into novel discoveries. (p. 92)

Action taken or to be taken

The Parent Project Muscular Dystrophy (PPMD) End Duchenne Grant Award Program is a successful partnership between NIH and PPMD to leverage private and public support to accelerate translational research for Duchenne muscular dystrophy (DMD). Projects funded through the PPMD program have gone on to successfully compete for NIH funds. For example, one project funded by PPMD, which is focused on developing the protein biglycan into a useable form to test as a therapy for DMD, was then funded through the National Institute of Neurological Disorders and Stroke (NINDS) translational research program. A second project, after receiving bridge funding through PPMD, was awarded a research project grant co-funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and NINDS. This project is focused on validating the use of MRI as a non-invasive biomarker for monitoring DMD disease progression and serving as an outcome measure for clinical trials.

NINDS, NIAMS, NICHD, and NHLBI support a broad portfolio of research, including the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRC), to translate research findings on DMD and other muscular dystrophies (MD) into new and improved therapies. From 2005-2010, investigators at the MDCRC at the Children's National Medical Center developed standard operating procedures for use of a mouse mutant that models DMD as a means of screening drugs for efficacy and safety. NIH-supported researchers have tested small molecules in cell-based assays and animal models and have demonstrated that these compounds show activity and functional improvement in animals. A number of these compounds are getting closer to being tested in clinical trials. Gene replacement therapy is another approach to treating DMD and NIH-supported investigators have made exciting progress on developing the most effective delivery method and vehicle for the reparative gene. NIH-funded investigators have also developed strategies to suppress or evade the immune response, which may be activated as a result of gene replacement therapy. Investigators at one of the MDCRCs funded by NICHD - the Research Institute at Nationwide Children's Hospital Research Center in Ohio - are

contributing to this effort by testing multiple strategies to overcome immunity, including using non-human primates to test whether depleting certain types of immune cells allows expression of the introduced gene. NIH-funded projects are also focused on genetic modification strategies to inactivate or skip genetic mutations, particularly those in the dystrophin gene that cause DMD. NIAMS recently funded a new Center of Research Translation (CORT), the CORT of Systemic Exon-Skipping in Muscular Dystrophy. The CORTs encompass a multidisciplinary approach and are made up of at least one basic and one clinical project. The new center will test the therapeutic potential of molecules that encourage cells' protein-producing machinery to bypass mutated segments of the dystrophin gene; if the molecules are effective, the cells should produce a modified, but functional, form of dystrophin.

In addition to research on DMD, NIH also supports projects focused on other forms of MD, including myotonic and facioscapulohumeral dystrophies. Research on one form may help inform research in other dystrophies, and one therapeutic approach may be applicable to multiple types of MD. Five large NIH-funded MD translational research projects have met current year milestones and are progressing toward Investigational New Drug applications to the FDA, which represents exciting progress toward the goal of developing effective therapies for these diseases.

Item

Network of Excellence in Neuroscience Clinical Trials. - The Committee commends NINDS for its leadership in creating the Network of Excellence in Neuroscience Clinical Trials [NEXT] program, which will create a robust, standardized and accessible infrastructure to facilitate rapid development and implementation of protocols in neurological disorders affecting adult and/or pediatric populations. NINDS has indicated that the first project to utilize the new NEXT infrastructure will be a biomarker validation study of spinal muscular atrophy [SMA]. Identifying one or more biomarkers for SMA would represent a significant step towards accelerating efforts to create effective treatments for this disease. The Committee also urges NINDS to continue to demonstrate strong support for translational research on SMA that will accelerate the development of therapies for testing in the clinic and facilitate the submittal of investigational new drug applications to the Food and Drug Administration. The Committee requests an update in the fiscal year 2013 congressional budget justification on the specific goals for the NEXT SMA initiative and its efforts relative to translational research on SMA. (p. 92)

Action taken or to be taken

Several novel treatments for SMA and other neurological disorders are approaching readiness for clinical testing, but the absence of infrastructure, including centralized resources, support for patient recruitment into trials, and standardized protocols and central IRBs are often a major impediment. Therefore NINDS is launching NeuroNext to address that early phase barrier. This clinical network is especially important for rare disorders, including pediatric diseases such as SMA (a muscle wasting disease that in its most severe form can cause death in infancy)), for which emerging scientific opportunities are encouraging but lack of infrastructure presents special challenges. The network will efficiently handle regulatory and contractual issues rapidly engage appropriate teams of researchers and clinical sites, decrease the time between trial design and execution, and reduce trial cost. The network protects intellectual property to encourage testing of the most promising candidate treatments, whether they arise from foundations,

industry, or academic therapy development programs. By maintaining support for clinical infrastructure and expertise, including clinical research coordinators, the network will reduce delays in building infrastructure for each new trial, improve the speed of enrollment of trial participants, foster the highest quality clinical research, and enable better choices of therapies for phase III clinical trials, another key issue for rare disorders such as SMA for which multiple candidate therapies are emerging. The resources and expertise of the multi-disease network are much greater than NINDS could dedicate to any single disease of the many within its mission.

Following active engagement of the research community, solicitations, and peer review of applications, in FY 2012 NINDS established the Data Coordinating Center and Clinical Coordinating Center for the NeuroNEXT network and funded 25 clinical sites across the United States. While development of the network was underway in FY 2011, the NIH and FDA jointly sponsored a scientific workshop bringing together researchers and disease advocates to discuss the development of biomarkers for SMA. Biomarkers are objective measures of the disease process and the activity of candidate therapeutics, so biomarkers can expedite therapy development. NINDS solicited proposals for an SMA biomarkers study in late FY 2011 and the study could begin in FY 2012 as the first clinical project of the network if meritorious applications are received. In FY 2012, NINDS also began soliciting novel therapeutic candidates for clinical trials, for SMA and other neurological diseases. Solicitations target academia, foundations, and industry, with the first clinical trials likely to begin in 2013.

As clinical testing moves forward, NIH continues to aggressively support preclinical development of therapies for SMA because the challenges of therapy development are so great and the success rate so low for any single therapeutic candidate, especially for neurological diseases. NIH supports multiple SMA therapy development projects via traditional investigator initiated research and through targeted programs, including the milestone-driven NINDS Cooperative Program for Translational Research. In 2010, an NIH workshop brought together representatives from NIH, private supported research teams, and disease advocates to discuss the encouraging pre-clinical progress in SMA drug, cell, and gene therapies, to deliberate key issues in SMA preclinical and clinical therapy development, and to prepare for future clinical trials.

Item

Stroke. - The Committee continues to prioritize research into the causes, diagnosis, treatment, recovery, rehabilitation and prevention of stroke. The Committee urges NINDS to foster innovative basic, clinical, translational and prevention stroke research for all age groups affected by stroke, including children and newborns, through all available mechanisms as appropriate. Further, the Committee notes that NINDS will manage a novel stroke planning effort beginning in 2011, building on the work of the Stroke Progress Review Group, to assess the current state of stroke research and develop priorities to advance the most promising areas in prevention, treatment, recovery, and rehabilitation research. The Committee requests an update on this initiative in the fiscal year 2013 congressional budget justification. (p. 92)

Action taken or to be taken

NIH prioritizes innovative and meritorious basic, clinical and translational research on stroke causes and mechanisms so new prevention, treatment and recovery strategies can be developed.

NINDS continues to invest heavily in stroke clinical research, including many studies to evaluate innovative approaches to treatment. One trial has the potential to vastly improve ischemic stroke treatment by testing a therapy for use in the very short time window when the potential to limit brain damage is at its highest. The Field Administration of Stroke Therapy - Magnesium (FAST-MAG) trial is investigating whether magnesium sulfate is neuroprotective when administered in the ambulance less than one or two hours after experiencing a stroke. MR WITNESS: A Study of Intravenous Thrombolysis with Alteplase in MRI-selected patients - is being conducted by Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) centers at Massachusetts General Hospital and the NINDS intramural program to optimize use of tissue plasminogen activator (tPA, the only FDA-approved treatment for ischemic stroke) by using brain imaging to identify time of stroke onset. If successful, this will allow tPA to reach patients who are currently excluded due to an unknown time of stroke. In a Small Business Innovation Research translational project, investigators at Pulse Therapeutics in Saint Louis, Missouri and the Washington University SPOTRIAS center are developing ways to enhance penetration of tPA into blood clots using magnetic particles and ultrasound waves.

Recent findings from two NINDS-supported clinical trials will have a significant impact on stroke clinical practice. In the Locomotor Experience Applied Post Stroke (LEAPS) trial, stroke patients who received intensive physical therapy improved their ability to walk as well as those treated with a more complex rehabilitation program involving a body weight-supported treadmill. In the Stenting versus Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) study, medical management was shown to be superior to the surgical intervention, an advantage due to a greater risk in the stenting procedure coupled with highly effective risk reduction using standard medical therapy.

NINDS also invests in stroke prevention research. In the Insulin Resistance Intervention after Stroke (IRIS) trial, investigators will determine whether a type 2 diabetes medication prevents recurrent stroke in patients with pre-diabetic insulin resistance. In one study involving children, investigators are exploring whether blood transfusion therapy can prevent silent strokes in children with sickle cell anemia, the primary cause of neurological complications in these patients. Investigators in another study will determine the role of infection in recurrent strokes in children with arterial ischemic stroke so that prevention strategies can be developed.

Basic research supported by NINDS includes studies of immune and inflammation responses that occur after a stroke and are thought to mediate the neuron damage. Investigations into cell death pathways and protective mechanisms imparted by surrounding cells are helping researchers identify targets for new stroke therapies. Basic and translational studies will also clarify mechanisms of stroke injury and repair in infants to minimize neurological consequences.

The Stroke Progress Review Group is conducting a final review of recent seminal stroke research advances and will identify unaddressed or new priorities for the field. In the second phase of this planning effort, which will begin in early 2012 and culminate in a summer meeting, NINDS will engage leading experts to distill the most pressing and opportune questions to be answered in stroke prevention, treatment and recovery research.

National Institute of Allergy and Infectious Diseases (NIAID)

Senate Significant Items

Item

Anti-Malarial Medicines. - The Committee encourages the Institute to continue supporting the work of institutions of higher learning in combating the health, economic and security impacts of malaria. The Committee encourages NIAID to increase its investment in public-private partnerships that are involved in research and development of anti-malarial medicines; the development of safe and effective drugs for malaria prophylaxis and treatment, including 8-aminoquinolines; new, effective pediatric formulations; and alternatives to artemisinin combination therapies in response to the rapidly emerging threat of artemisinin resistance. (p. 93)

Action taken or to be taken

Malaria, caused by several *Plasmodium* parasites and transmitted by mosquitoes, continues to be the most important tropical parasitic disease in terms of annual mortality worldwide. NIAID supports basic and translational research essential for improved understanding of the biology and effective treatment of malaria. NIAID remains committed to research and development of new diagnostics, treatments, and vaccines for malaria. Partnerships between NIAID, other governmental and non-governmental organizations, academic institutions, and private industry will play a crucial role in translating basic science discoveries into anti-malarial therapies.

To address the global public health problem of high mortality due to childhood malaria, the NIAID intramural research program has initiated a new effort focused on malaria immunology and pathogenesis in pregnant women and young children. The need for this effort was made apparent by the finding of NIAID intramural researchers and colleagues that the risk of childhood malaria is related to prenatal exposure to malaria through infected mothers, as well as other host factors. In addition, NIAID intramural researchers are working to develop alternate transmission-blocking drugs that are as potent as the 8-aminoquinolines but which do not cause anemia in a subset of the population.

NIAID scientists also continue to search for new and effective anti-malarial drugs to combat growing drug resistance, screening nearly 3,000 chemicals for activity against various malaria parasites and identifying 32 highly active compounds. A high-throughput drug screen conducted by NIAID intramural investigators in partnership with the Medicines for Malaria Venture has also identified chemical compounds that kill malaria parasites by blocking a pathway required for nutrient acquisition. These compounds will be further investigated as candidate anti-malarial medicines. The NIAID intramural research program also includes ongoing studies of anti-malarial drug resistance, an increasing challenge to effective malaria control worldwide. In Southeast Asia and Africa, where artemisinin combination therapies are first-line treatments against malaria, NIAID investigators are working with local scientists to define the response to artemisinin. This project will build local research capacity and inform future approaches to counter artemisinin resistance and improve malaria treatment in these areas. In November 2010, NIAID and the Fogarty International Center convened the *Artemisinin Resistant Malaria: Research Challenges, Opportunities, and Public Health Implications* meeting, which brought together a broad array of stakeholders to address the growing challenge of resistance to

artemisinin combination therapies and to promote collaborations translating new scientific findings into anti-resistance efforts.

Public-private research collaborations supported by NIAID are making strides in investigating new anti-malarial medicines. For example, an NIAID-supported academic researcher affiliated with a major pharmaceutical company is investigating spiroindolones, a new class of anti-malarial drugs with a novel mechanism of action. One of these drugs has demonstrated the ability to rid mice of malaria-causing parasites after a single oral dose. Further tests in animals and humans are planned to determine whether the drug will advance to later stages of development by the pharmaceutical company. In addition, NIAID has participated in a successful joint effort with the public-private partnership Medicines for Malaria Venture. The extramural partnership has characterized a promising target for anti-malarial therapies, dihydroorotate dehydrogenase, and identified a candidate drug for further study and product development. This project, as well as other research partnerships to investigate the development of new and improved anti-malarial medicines, will remain an important component of NIAID's malaria research program. These efforts, as well as NIAID's commitment to the development of vaccines and other malaria control strategies, will continue to make progress in addressing the global public health challenge of malaria.

Item

Food Allergies. - The Committee is pleased that NIAID has convened periodic expert panels on food allergy research since 1996 to make key recommendations to investigate the natural history of food allergy in young children who have risk factors predisposing them to develop food allergy; resolve impediments to clinical trials design and conduct; and perform clinical trials using food allergens, given orally or sublingually, to treat existing food allergy. The Committee is aware that public and private research to develop immunotherapies is progressing to an advanced clinical trials stage with the consensus support of the Nation's leading food allergy research institutions. NIAID is strongly encouraged to support this stage of the research, which has the potential to cure food allergies. (p. 93)

Action taken or to be taken

In FY 2011, NIAID provided \$28 million in support of food allergy research, approximately a 20-fold increase when compared to FY 2003. This investment has supported basic, translational, and clinical research leading to improvements in our understanding of the mechanisms of food allergy and the development of promising approaches such as oral or sublingual immunotherapy to treat and prevent food allergy.

NIAID is aware of the interest of private donors and foundations to conduct large-scale clinical trials that use immunotherapy for the treatment or prevention of food allergy. The results of these trials could lead to licensure of drugs and food extracts by the U.S. Food and Drug Administration. However, more must be learned about the mechanisms of action of, and appropriate candidates for, immunotherapy. NIAID, the Consortium of Food Allergy Research (CoFAR), cosponsored by NIAID and NIDDK, and the NIAID Immune Tolerance Network (ITN) have met with private donors and foundations to discuss options to conduct complementary immunological/mechanistic studies as components of these clinical trials.

Currently, CoFAR is developing new immunotherapeutic approaches to prevent IgE-mediated food allergy, including food allergy-associated anaphylaxis. CoFAR is conducting three clinical trials to determine whether oral immunotherapy for egg allergy is safe and effective in children 5 to 18 years old; to determine whether peanut extract placed under the tongue is a safe and effective treatment for adolescents and adults with peanut allergy; and to assess the safety and efficacy of administering modified peanut allergens in the form of a rectal suppository as a treatment for peanut allergy. The ITN also is conducting a peanut allergy prevention trial in infants 4 to 10 months of age at time of enrollment to determine if oral peanut consumption prevents the development of peanut allergy by age 5 years.

In FY 2012, NIAID will continue evaluating potential immunotherapy protocols for clinical implementation in children and adults with food allergy. NIAID will sustain its strong commitment to food allergy research, including immunotherapy clinical trials for treatment or prevention. In addition, NIAID will continue its partnerships with private donors and foundations with an interest in food allergy research and research collaborations.

Item

Hepatitis B Virus [HBV]. - The Committee applauds NIAID's efforts to pursue the development of new classes of drugs that are safe and effective in treating HBV. The Committee urges continued HBV research on different courses of treatment as well as ways to support efforts to identify new cellular and antiviral targets and develop new strategies for intervention. The Committee also urges an increased focus on pregnant women and pediatric cases of hepatitis B. (p. 93)

Action taken or to be taken

Hepatitis B virus (HBV) is responsible for the majority of the worldwide hepatitis burden, with HBV-related liver cancer and cirrhosis resulting in thousands of deaths in the United States and hundreds of thousands of deaths worldwide. NIAID pursues research to develop new classes of drugs to treat HBV infections that work by different mechanisms than the currently licensed products. Through both solicited research programs and investigator-initiated research, NIAID supports the investigation of novel cellular and antiviral targets against HBV. This research will further the development of new candidate therapeutic drugs to treat chronic HBV infection in affected populations, including pregnant women and pediatric populations.

NIAID supports a number of research grants to conduct basic research and to develop novel therapies for HBV. NIAID-supported researchers are at the early stages of developing therapies that target the HBV surface antigen, viral capsid, HBV covalently closed circular DNA (cccDNA), as well as the host's innate immune system. NIDDK investigates hepatitis B treatments for adults and children in its Hepatitis B Research Network. The Network comprises 23 adult and 10 pediatric sites to study disease processes and natural history, as well as to develop effective approaches to treatment of chronic HBV infection. The Network plans to enroll pregnant women with hepatitis B to assess the feasibility of conducting a clinical trial of antiviral therapy in pregnant women at high risk for transmission of HBV to their newborns.

In FY 2011, NIAID funded three new research projects focused on novel HBV therapeutics through the *Partnerships for Development of New Therapeutic Classes for Select Viral and Bacterial Pathogens* initiative. These awards will help advance the development of new classes of drugs to treat HBV. NIAID also offers a broad array of pre-clinical and clinical research resources and services to researchers in academia and industry. By providing these critical services to the research community, NIAID can help to bridge gaps in the product development pipeline and lower the financial risks incurred by industry. For example, NIAID supports contracts to conduct *in vitro* screening of candidate drugs against HBV as well as hepatitis C virus. In FY 2011, 230 compounds were screened for antiviral activity against HBV.

NIAID further evaluates promising drug candidates in appropriate animal models. Candidate HBV drugs with novel mechanisms of action, as well as new therapies to help the immune system fight HBV infection, are screened and evaluated through animal contracts supported by NIAID. Animal models for HBV infection supported by NIAID in FY 2011 include a transgenic mouse model and a woodchuck infection model considered to be the gold standard for pre-clinical HBV drug studies. These models are critical tools in the identification of new HBV drug targets and the development of new therapeutic strategies to treat HBV infection. Candidate therapies are evaluated singly for effectiveness against chronic HBV or in combination with current drugs.

NIAID will continue to support its diverse research program on HBV, with emphasis on the development of novel therapies to combat chronic HBV infection, including strategies for specific groups including pregnant women and pediatric populations.

Item

Immunotherapy. - The Committee is aware of research showing that broader use of immunotherapy for the treatment of allergic rhinitis could improve clinical outcomes and significantly reduce healthcare costs. Additional research is needed to examine the clinical and economic impact of immunotherapy in both children and adults. The Committee encourages NIAID to collaborate with AHRQ and the Centers for Medicare and Medicaid Services on the development and support of a research initiative on this topic. (p. 93)

Action taken or to be taken

Currently, allergen immunotherapy is not a first-line therapy for the treatment of allergic rhinitis due to several challenges, including significant risk of systemic allergic reactions (anaphylaxis) and the lack of standardized, demonstrably effective allergenic extracts for immunotherapeutic use. In addition, immunotherapy requires frequent dosing and prolonged treatment and must be administered by expert physicians in clinical settings, further limiting its wide use as a first-line therapy.

NIAID is actively exploring the potential benefits and risks of immunotherapy for the prevention and treatment of allergic rhinitis (AR) and asthma, through studies being conducted by its Immune Tolerance Network (ITN) and Inner City Asthma Consortium (ICAC). An ongoing ITN clinical trial is focusing on allergen immunotherapy comparing subcutaneous (injection) to sublingual immunotherapy with grass allergen in adults with allergic rhinitis. ICAC researchers

are developing new monitoring tools and guidelines to standardize the treatment of allergic rhinitis, and investigating the role of allergic rhinitis as an asthma co-morbidity. ICAC previously identified cockroach allergy as a major risk factor for asthma severity in poor, urban environments, and has focused on the development of cockroach allergy immunotherapy. In the last several years, ICAC has collaborated with the U.S. Food and Drug Administration on comparative studies of commercially available cockroach allergen extracts for use in immunotherapy. ICAC also has completed safety studies of sublingual and subcutaneous cockroach immunotherapy in adults and children. Further study of higher doses of sublingual cockroach immunotherapy in children with allergic rhinitis is ongoing.

The NIAID Allergen and T Cell Reagent Resources initiative aims to identify appropriate immune system targets to improve allergen immunotherapy for allergic rhinitis, asthma, and food allergies. In FY 2012, this initiative will be recomputed as the NIAID Allergen Epitope Research and Validation Centers program.

NIAID concurs that it is important to determine the most appropriate, efficacious, and cost-effective treatment for allergic rhinitis in children and adults. In December 2010, NIAID, in conjunction with national and international scientific experts, held a two-day workshop on allergen immunotherapy to discuss its strategic plans for this research. In FY 2012, NIAID will re-convene this expert workshop to discuss new research findings and to explore novel forms of immunotherapy. NIAID scientists are serving as consultants to the Agency for Healthcare Research and Quality (AHRQ) in support of AHRQ's comparative effectiveness evaluations of allergic rhinitis treatments and of allergen immunotherapy in allergic rhinitis. NIAID plans to initiate a discussion with AHRQ and the Centers for Medicare and Medicaid Services to discuss shared interests in allergen immunotherapy.

Item

Kidney Transplantation. - As the demand for suitable kidneys for transplantation continues to far exceed the supply, the Committee is pleased to learn that research funded by NIAID has resulted in the establishment of desensitization protocols that have successfully demonstrated an increase to the suitability of a larger number of cadaver kidneys for transplantation for highly sensitized candidates, who are the sickest and most difficult to match on the kidney transplant waiting list. The Committee therefore urges NIAID to support a multi-center initiative with a companion data collection and analysis center to facilitate the use of this protocol at an increasing number of transplant centers across the country. (p. 93-94)

Action taken or to be taken

Many individuals in need of an organ transplant experience a type of immune system activation known as "presensitization." Due to previous blood transfusions, pregnancy, or transplants, their immune systems generate harmful antibodies that would attack transplanted organs, leading to organ rejection. "Desensitization" works by removing these harmful antibodies from the blood prior to surgery, in an effort to improve the likelihood of a successful transplant outcome.

NIAID continues to support research on desensitization protocols with the goal of making organ (including kidney) transplantation available to highly sensitized transplant candidates. To date,

however, the results of these studies have been inconclusive. Before a multi-center desensitization initiative for kidney transplantation can be undertaken, more must be learned about the desensitization process, including its mechanisms of action and which patients are most likely to benefit from the process.

Currently, NIAID and NHLBI are conducting two multi-center clinical trials in the Clinical Trials in Organ Transplant Consortium (CTOT) and the Clinical Trials in Organ Transplantation in Children Consortium (CTOT-C) that address the issues of sensitized organ transplant candidates. CTOT investigators are evaluating an innovative desensitization regimen using the cancer drug Bortezomib in presensitized adult heart transplant recipients. CTOT-C investigators are studying the effects of a widely-used desensitization regimen that includes intravenous immunoglobulin and plasmapheresis on the outcome of presensitized pediatric heart transplant candidates. The results of these studies will inform the design and conduct of future desensitization transplantation protocols, including kidney transplantation, in adult and pediatric populations.

NIAID will continue its efforts to evaluate the appropriateness of desensitization protocols for widespread clinical implementation. In FY 2013, NIAID will recompile the CTOC-C program and welcome proposals to evaluate desensitization regimens.

Item

Microbicides. - With NIH and USAID leadership, proof of concept has been established for an antiretroviral [ARV]-based microbicide to prevent HIV infection in women. The Committee encourages NIAID to coordinate with USAID, the State Department, other Federal agencies and global donors to prioritize and expedite microbicide development efforts with the goals of enabling regulatory approval of the first effective microbicide and providing support for efficacy trials of new and complementary ARV-based microbicides. (p. 94)

Action taken or to be taken

The NIH Office of AIDS Research (OAR) coordinates microbicide research activities across NIH and the Federal government. OAR convenes the Trans-NIH Microbicide Coordinating Committee which includes all of the Institutes and Centers that conduct or support microbicides and microbicides-related research (NIAID, NICHD, NIMH, NCI, FIC, NIAAA, NIDA, NINR, NCATS) to facilitate coordination of NIH microbicides research activities. OAR established and chairs a Trans-Governmental Microbicide Coordinating Committee, comprised of NIH Institutes and Centers, the Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration (FDA), the Department of Defense, the Department of Veterans Affairs, and the U.S. Agency for International Development (USAID), to facilitate coordination and collaboration of USG microbicides-related research activities. OAR also convenes governmental and non-government experts from academia, industry and the HIV community to develop the annual Trans-NIH Plan for HIV-Related Research. The Plan, which includes the strategic plan for microbicide research and development, is used to inform budget allocations based on research priorities. In addition, OAR established and serves as the Secretariat for the Microbicides Research Working Group (MRWG), an independent non-governmental panel of experts that advises the NIH and other entities that support microbicide research and

development. OAR also works with external experts to ensure an efficient, integrated, and cost-effective approach to microbicides research that limits unnecessary duplication of effort.

NIH, including NIAID, continues its strong support of research to identify and develop safe, effective, and acceptable microbicides to prevent HIV infection. NIAID's highly integrative program provides support for basic sciences research through preclinical development and clinical trials that facilitate product regulatory approval. In 2010, with NIH and NIAID infrastructure support, the Centre for AIDS Programme of Research in South Africa microbicide trial (CAPRISA 004) demonstrated proof of concept that a vaginal microbicide could prevent HIV infection. Other recent NIH-funded studies have also provided evidence for the use of topical microbicides as an HIV prevention tool. These include: RMP-02/MTN-006, a Phase I study carried out in a collaboration between the Rectal Microbicide Program and the Microbicide Trials Network (MTN) that demonstrated that tenofovir gel had a strong antiviral effect when used in the rectum; and MTN-001, a Phase II study that found that daily use of the vaginal gel for six weeks led to a higher concentration of active drug in the vagina than did the oral tablet. Product safety studies for topical microbicides that can be used during pregnancy also are carried out through the MTN.

NIAID is working with CDC, the International Partnership for Microbicides (IPM), and CONRAD to coordinate a number of projects supported by NIAID's Integrated Preclinical-Clinical Program for HIV Topical Microbicides and Microbicide Innovation Program. These two programs support the development of promising products and technologies that may advance into clinical trial evaluation through the MTN, the HIV Prevention Trials Network, or other clinical research entities. The MTN, supported by NIAID, NICHD, and NIMH, collaborates with USAID, IPM, and CONRAD as well as other microbicide sponsors and donors, such as the Bill and Melinda Gates Foundation (BMGF), to test the most promising microbicides for safety and effectiveness. NIAID will continue to collaborate with academia, industry, and foundations to identify and explore new and existing microbicide compounds and delivery methods. For example, in 2012, the MTN will implement a novel Phase III safety and effectiveness study of dapivirine delivered in a vaginal ring in collaboration with Tibotec, IPM and BMGF.

Through the MTN, NIAID is supporting the ongoing Vaginal and Oral Interventions to Control the Epidemic (VOICE) study, or MTN-003. VOICE is a Phase IIb microbicide study designed to evaluate oral and topical ARV-based approaches to prevent HIV transmission. The study was recently modified because an interim review found that the intravaginal gel, an investigational microbicide, as well as oral tenofovir (Viread®), were not effective among study participants. The study will continue to evaluate the safety, effectiveness, and acceptability of daily oral tablets containing tenofovir plus emtricitabine (Truvada®). The VOICE study began in September 2009 and originally enrolled more than 5,000 HIV-uninfected women in Africa. The final study results are anticipated in early 2013.

Item

Tuberculosis [TB]. - The Committee notes the recent development of GeneXpert, the new TB diagnostic test that holds the potential to dramatically improve TB diagnosis, treatment and

control. The Committee applauds NIAID for its continued attention to the development of new TB diagnostics, drugs and vaccines. (p. 94)

Action taken or to be taken

Despite the availability of drugs and a vaccine, tuberculosis (TB) continues to kill millions of people worldwide each year. The significant global public health challenge of TB is intensified by the emergence of multidrug-resistant and extensively drug-resistant forms of TB as well as the increasing incidence of TB/HIV co-infection.

NIAID pursues research on tools to diagnose, treat, and control TB. A new TB diagnostic was recently developed with NIAID support and has been endorsed for widespread use by the World Health Organization. Cepheid's Gene Xpert MTB/RIF assay provides accurate results for the rapid diagnosis of TB, multidrug-resistant TB, and TB in HIV-infected individuals. This rapid test will assist in diagnosis of TB and help determine the optimal treatment for cases of drug-resistant TB or TB/HIV co-infection.

NIAID supports a broad range of basic and clinical research on TB. NIAID also provides resources to the TB research and product development community, including screening for drugs against TB and evaluation of potential TB vaccine candidates in appropriate animal models. NIAID has supported efforts to improve current TB therapies as well as Phase I and II clinical trials investigating novel TB drugs. In its intramural programs, NIAID pursues, among other studies, research to understand the metabolism of latent TB, to investigate new TB antibiotics, and to develop and utilize animal models for predicting the outcome of human TB therapies.

NIAID's investments in basic science have contributed to TB diagnostics and vaccines currently in clinical development. NIAID is investigating new protocols for rapid, sensitive diagnosis of active TB infection and drug-resistant TB, including assessments of the performance of early-stage TB diagnostics in Uganda, South Africa, Korea and Brazil. In addition, NIAID has contributed data critical for the development of a novel vaccine containing the TB H56 protein produced during latent infection. The vaccine, tested in mice and found to be protective against TB, is now entering clinical development. Through the NIAID-supported Tuberculosis Research Unit, researchers are conducting clinical studies of TB to increase our understanding of the disease and contribute to improvement of diagnostic, preventive, and curative strategies.

NIAID also pursues research on improved TB treatment protocols. NIAID has developed critical international collaborations in South Korea to pursue clinical studies of two drugs repurposed for treatment of drug-resistant TB. In the case of TB/HIV co-infection, the NIAID-supported CAMELIA/ANRS 1295 study found a 34 percent decrease in mortality for patients co-infected with HIV and TB when antiretroviral therapy to treat HIV was initiated earlier than the current standard. Altering treatment regimens to reflect the findings of this study has the potential to greatly reduce TB-associated mortality in HIV/TB co-infected patients. To build upon these and other findings in TB/HIV co-infection, NIAID will support clinical studies evaluating the Gene Xpert MTB/RIF Assay for rapid diagnosis of TB and TB rifampin resistance in HIV-infected and uninfected patients.

NIAID will continue to provide support for investigator-initiated, basic, and translational TB research. NIAID's sustained investment in technology development and data interpretation will lead to the development of improved diagnostics, drugs, vaccines, and intervention strategies for combating TB.

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National Institute of General Medical Sciences (NIGMS)

Senate Significant Items

Item

Behavioral Research. - The Committee applauds the leadership of NIGMS in the development of the OppNet collaboration on basic behavioral and social science research, and it encourages NIGMS to maintain its commitment to that trans-NIH initiative. The Committee also commends NIGMS's program of research on the efficacy of interventions to promote research careers, such as its studies on effective mentoring and career transitions. (p. 94)

Action taken or to be taken

NIGMS continues to actively support the OppNet Initiative, with program and administrative staff contributing to the development of trans-NIH funding opportunity announcements and the Coordinating Committee's funding decision process for existing announcements. In addition, the NIGMS Advisory Council approved an NIGMS staff developed concept clearance entitled "Modeling Social Behavior," at its September 2011 meeting. This concept will be developed over the course of the next several months into a new program announcement to encourage and support research that applies mathematical, engineering, and computational systems approaches and methods to understanding basic behavioral and social phenomena.

Further, several NIH Institutes, including NIMH and NIGMS, currently administer OppNet grants that focus on biological approaches to behavioral research. For example, an NIMH grant explores the psychological and neural mechanisms that underlie the relationship between motivation and cognitive control. Another project is examining the role of specialized cells in promoting adaptive or nonadaptive responses to stress. This research will provide insight into cellular mechanisms associated with resilience to stress. As a result, the research may help to identify targets for therapeutic development.

Regarding the program on Research to Understand and Inform Interventions that Promote the Research Careers of Students in Biomedical and Behavioral Sciences, NIGMS plans to reannounce the RFA annually. NIGMS received approval from the National Advisory General Medical Sciences Council to continue the initiative for another five years.

Item

Institutional Development Awards [IDeA]. - The Committee recognizes the importance of the Centers of Biomedical Research Excellence and the IDeA Networks of Biomedical Research Excellence programs, which are essential components to the overall success of the IDeA program. The focus of IDeA should continue to be on improving the necessary infrastructure and strengthening the biomedical research capacity and capability of research institutions within the IDeA States. (p. 94)

Action taken or to be taken

NIH appreciates the Committee's recognition of the importance of the Institutional Development Award (IDeA) program and its two main programmatic components, the Centers of Biomedical

Research Excellence (COBRE) and IDeA Networks of Biomedical Research Excellence (INBRE), to its overall success. The IDeA program strengthens the Nation's research infrastructure by broadening the geographic distribution of NIH funding for biomedical and behavioral research.

The COBRE and INBRE initiatives will continue to foster the development of capacity and infrastructure, with the aim of affording an increasing number of investigators in IDeA states the ability to compete successfully for more traditional NIH funding, particularly in areas of basic biomedical research. A new funding opportunity, the IDeA Infrastructure Program for Clinical and Translational Research (IDeA-CTR), has been announced to stimulate translational research activities within the IDeA States.

Conference Significant Items

Item

Institutional Development Awards [IDeA]. - The conferees provide \$276,480,000 to increase support for the Institutional Development Awards (IDeA) program. The conferees recognize the importance of the Centers of Biomedical Research Excellence (COBRE) and the IDeA Networks of Biomedical Research Excellence (INBRE) programs. The conferees believe the IDeA program has made a significant contribution to biomedical research and creating a skilled workforce. Therefore, the conferees provide a \$45,882,000 increase and recommend it be divided equally toward a new COBRE competition and to support new awards for the IDeA Clinical Trial and Translation Program to develop infrastructure for clinical and translational research in IDeA States. The conferees encourage the NIH Director to expand the program to support co-funding of IDeA projects across NIH ICs to foster the development of efforts in IDeA State programs. Further, as an Office of Experimental Program to Stimulate Competitive Research (EPSCoR) program, the focus of IDeA should continue to be on improving the necessary infrastructure and strengthening the biomedical research capacity and capability of research institutions. Unfortunately, many institutions in EPSCoR-qualifying states who could benefit from the IDeA program are ineligible for funding. The conferees encourage NIH to revise current eligibility criteria to take into account how the decreasing success rate for RO1 grants NIH-wide is affecting IDeA eligibility. In particular, the conferees believe the IDeA Director should have the authority to consider funding institutions in any State that is EPSCoR eligible. The conferees urge NIH to develop criteria to incorporate flexibility into the program to address these concerns. The conferees request an update on both the IDeA eligibility criteria proposals and funding level by State and major activities, to include the co-funding activity, in the fiscal year 2013 congressional budget justification. (p. 37)

Action taken or to be taken

The COBRE and INBRE initiatives will continue to foster the development of capacity and infrastructure, with the aim of affording an increasing number of investigators in IDeA states the ability to compete successfully for more traditional NIH funding, particularly in areas of basic biomedical research. To expand the COBRE program, the IDeA program will fund new Clinical and Translational Research centers to support the development of infrastructure and other resources required for the conduct of clinical and translational research in IDeA-eligible states.

NIH will also explore the expansion of research support within EPSCoR-qualifying states and across NIH ICs.

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National Institute of Child Health and Human Development (NICHD)

Senate Significant Items

Item

Adverse Pregnancy Outcomes. - The Committee is pleased with the progress NICHD has made to identify women at risk for long-term morbidity, as women with severe, early adverse pregnancy outcomes are at increased risk for chronic health problems. The Committee encourages NICHD to continue developing strategies to prevent long-term adverse outcomes in these women. (p. 95)

Action taken or to be taken

NICHD has long been committed to identifying and developing strategies to prevent long-term adverse outcomes for women with pregnancy complications. Increasing evidence indicates that pregnancy and its outcomes may predict, or even influence, long-term maternal health. Improvements in women's health during pregnancy can improve lifelong health for women and their families.

In late 2010, NICHD and NHLBI cosponsored a workshop on the long-term cardiovascular effects of preeclampsia, *Bridging Preeclampsia and Future Cardiovascular Disease* (<http://www.nhlbi.nih.gov/meetings/workshops/bridging-pe.htm>). The purpose of bringing together scientific experts in the fields of cardiology, maternal-fetal medicine, and epidemiology was to examine the associations between preeclampsia and future cardiovascular disease, with the goal of identifying research gaps that could lead to prevention of these outcomes.

In response to the *Bridging Preeclampsia* meeting, NICHD is exploring whether research on the long term effects of pregnancy complications can be performed in a cost-effective manner using existing cohorts of women. A major clinical trial of 10,000 women in their first pregnancy recently has been completed, conducted by the NICHD's Maternal Fetal Medicine Units Network. All patients who had at least one elevated blood pressure reading underwent a rigorous chart review to identify cases of preeclampsia, pregnancy-induced hypertension and eclampsia. The trial showed that taking additional Vitamins C and E did not help prevent preeclampsia. Other data from the study are still being analyzed to identify common factors among the women experiencing those conditions.

The "Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (NuMoM2b)," is another ongoing study supported by NICHD to focus on methods to predict and mechanisms underlying adverse pregnancy outcomes such as preterm delivery, preeclampsia, poor fetal growth and stillbirth for women in their first pregnancy. Approximately 10,000 women will be enrolled as early as their eighth week of pregnancy, and evaluated with detailed clinical and ultrasound assessments throughout pregnancy. The pregnant women in the NuMoM2b study comprise an ideal population to study the development of chronic health problems and, potentially, find ways to intervene to prevent chronic diseases such as hypertension, cardiovascular disease, and diabetes.

In addition, increasing evidence shows that multiple births are associated with adverse health outcomes for both the mother and her offspring. Some infertility treatments, such as assisted reproductive technologies (ART) and non-ART ovulation stimulation protocols are associated with a higher incidence of multiple gestations; approximately 40 percent of all multiple gestations in the U.S. today result from infertility treatments. To this end, NICHD is supporting a clinical trial to identify ovarian stimulation treatments that minimize the incidence of multiple gestations, with the objective of minimizing the multiple birth rate from such treatments.

Item

Chromosome Abnormalities. - The Committee appreciates recent accomplishments by NIH in addressing the science of dosage-sensitive and insensitive genes. The Committee now urges NIH to leverage these efforts to achieve the translational science goal of producing detailed clinical data that can both move the science forward by being useful to researchers and assist clinicians in working with affected individuals and their families. The Committee also acknowledges and appreciates the ongoing NIH activities related to genetic disorders but urges new funding to support independent investigators whose work can provide pilot data or insight into future directions for the study of chromosome abnormalities, particularly those involving chromosome 18. (p. 95)

Action taken or to be taken

NICHD supports studies that identify critical genes within regions that represent chromosome abnormalities. In the past, these chromosome differences have been identified by routine karyotype techniques that look for large regions of missing or duplicated genetic material by photographing and magnifying the chromosomes isolated from single cells. New DNA-based technologies allow identification of much smaller regions of chromosome difference, known as copy number variants (CNVs), which are too tiny to be seen under a microscope using karyotype techniques. These CNVs are likely to underlie a significant proportion (perhaps up to 20 percent) of unexplained developmental delay, intellectual disability, autism, and multiple birth defects. As initially reported last year, work continues on the creation, implementation, and dissemination of a comprehensive atlas of CNVs. This atlas will provide scientists with unprecedented opportunities to characterize the genotype and phenotype variations associated with chromosomal disorders affected by differences in CNVs, ultimately benefitting large numbers of families with children with special needs.

NICHD continues to support research regarding duplications and deletions of segments of chromosomal material that include specific contiguous genes on critical chromosomes such as 21 and 18 that are associated with specific patterns of developmental delay and multiple malformations. Down syndrome, caused most frequently by the presence of an extra copy of chromosome 21, has enjoyed increased research interest since the release of the NIH Research Plan on Down Syndrome in 2007. In addition, three Program Announcements issued by NICHD are encouraging grant applications that focus on co-morbid conditions often affecting individuals with Down syndrome during adolescence. In December 2010, NICHD and the Global Down Syndrome Foundation cosponsored a meeting to discuss the research resources needed to stimulate and advance Down syndrome research, to include a patient contact registry, a research database, and a biobank. Out of that conference and other related meetings, as well as responses

received to the Requests for Information solicited by NIH (over 2000), the need for a Down Syndrome Consortium emerged. The first meeting of this new group, composed of investigators, members of national medical societies, patient advocacy groups, parents, self-advocates, and members of the trans-NIH Down Syndrome Working Group, was held in September 2011. The Consortium will promote the development of contact registries and research databases through the establishment of subcommittees that will involve both individuals from the Consortium and those with special expertise selected to serve on an ad hoc basis. Another major focus for the first one or two years will be the assessment of progress made in the implementation of the Research Plan on Down Syndrome.

NICHD also will continue its support of investigator-initiated research studies that focus on other contiguous gene disorders, although the number of grants funded largely depends on the quality of the applications submitted to NIH. NICHD-funded Rare Disease Clinical Research Center Consortium for Rare Epigenetic Disorders continues to support research on Angelman, Rett, and Prader-Willi syndromes. In addition to this center's longitudinal study of the natural history of more than 1000 individuals with these disorders, investigators have recently turned their attention to the study of sleep disorders experienced by these individuals, to determine which co-morbid factors such as obesity or abnormal respiratory control may contribute to these issues. Collectively, these studies will provide the knowledge base that informs the development of new diagnostics and therapeutics for individuals with continuous gene conditions.

Item

Demographic and Economic Research. - The Institute's investment in population representative longitudinal studies, such as the National Longitudinal Study of Adolescent Health, the National Longitudinal Study of Youth Child Supplement and Panel Study of Income Dynamics has yielded groundbreaking scientific research and served as a model for making publicly funded research data widely available, spurring cost-effective research in numerous disciplines and across multiple institutions. The Committee urges NICHD to continue investing in these large-scale population data sets and to sustain support for critical research infrastructure for demographic and behavioral population science. (p. 95)

Action taken or to be taken

NICHD recognizes the importance of longitudinal population studies and has supported a myriad of such research and training projects. In the past year, numerous studies revealed major scientific findings that significantly inform our understanding of human populations and health, demographic change, and behavioral and social science. For example, results from the National Longitudinal Study of Adolescent Health ("Add Health") suggest that about one in five young adults aged 24-35 have hypertension (high blood pressure). The study also indicated that their health care providers had previously told only about half of these young adults that they had high blood pressure. This is one of many informative findings generated by Add Health, a nationally representative sample followed from grades 7-12 since the 1990s.

Several other studies long supported by NICHD have advanced our knowledge of genetic influences on families, such as the Fragile Families and Child Wellbeing Study. Using data from this representative, longitudinal study of new mothers and their children, researchers have

advanced our understanding of the links between genes and postpartum depression, examining how two variations of the serotonin transporter gene (5-HTT) interact with socioeconomic status, as measured by education. They found evidence that women with large numbers of reactive 5-HTT alleles were more reactive (respond more strongly) to environmental exposures. Within this group of women, those with low education levels were more likely to suffer postpartum depression, and those with higher education levels were less likely to suffer from postpartum depression.

A longitudinal study of preschoolers' language-based bedtime routines, such as singing, reading, and storytelling found lasting positive benefits for children's sleep duration and cognitive development. However, these routines did not appear to benefit the children's behavior.

New data from a longitudinal, representative study of over 4,000 children show that growing up in poor neighborhoods – characterized by high poverty, low adult educational attainment, unemployment, and welfare receipt – throughout childhood can have a devastating effect on children's eventual educational attainment. The study found that compared to growing up in affluent neighborhoods, growing up in neighborhoods with high levels of poverty and unemployment reduced the chances of high school graduation for African American youth from 96 percent to 76 percent. The impact on white children was found to be only slightly less harmful.

NICHHD remains committed to investing in longitudinal studies and data sets such as these with the aim of advancing our understanding of the environmental influences on children's development, with or without the interplay of genetics, including how these factors affect health and wellbeing across the lifespan. In addition, the Institute is planning to award grants in the coming fiscal year for its trans-disciplinary population centers program to increase the impact and cost-efficiency of population science research.

Item

Learning and School Readiness. - The Committee recognizes the important contribution of NICHHD in establishing the scientific foundation of the development of reading, math and science skills that are critical to maintaining the Nation's competitiveness in math and science achievement. (p. 95)

Action taken or to be taken

NICHHD appreciates the acknowledgement of the importance of early learning and ongoing development, especially in the critical areas of reading, math, and science. The Institute's investigator-initiated research on learning and learning disabilities addresses these issues from birth into early adulthood, both for typically developing individuals and those with learning disabilities. Basic research in brain and cognitive development from infancy through young adulthood is critical to understanding human perception, memory, attention, problem-solving, and executive function (short-term memory, planning and organization of information, focusing attention, and mental flexibility).

In addition to funding investigator-initiated research, NICHD supports a Learning Disabilities Research Centers consortium, a consortium on math learning and learning disabilities, and a network of researchers who are exploring the most effective learning interventions for economically disadvantaged four-year-old English learning preschoolers. In the past year, the Institute has sponsored three scientific workshops to bring together experts in the field from across the country. The first workshop focused on executive function in preschoolers and was aimed at examining what is known about crucial cognitive function in early development, which is foundational to learning, and to identify research gaps. The second workshop centered on the intersection of math and reading learning disabilities, which frequently occur in the same child. The third workshop concentrated on cognition and learning in incarcerated youth, a significant but understudied segment of the population with learning problems. Publications summarizing the findings of the workshops and future research opportunities are in preparation.

Research findings from NICHD-supported grantees continue to be published in top-tier scientific journals, including citations in the August 19, 2011, special issue of the journal *Science*, “Investing Early in Education”. Additionally, NICHD staff in collaboration with an NICHD-funded investigator organized a special issue of *Behavior Genetics* (January 2011) focused on the genetics of language and reading development that included contributions from NICHD and NIH-sponsored research (<http://springerlink.com/content/0001-8244/41/1>). These and other research findings are broadly disseminated to educators, pediatricians, parents, and the public.

Item

Maternal Morbidity. - Though maternal morbidity rates are rising, the Committee understands that there are no uniform definitions of severe maternal morbidity. The Committee encourages NICHD to hold a consensus workshop to identify such definitions, which would help Federal, State and local agencies and research institutions establish standardized and interoperable processes for surveillance, data collection and research. (p. 95)

Action taken or to be taken

NICHD appreciates the complexity of uniform definitions of severe maternal morbidity. Given the impact on women, families, and communities of maternal mortality, more research is needed on the morbidities that may both underlie and precipitate mortality. Examples of these morbidities include postpartum hemorrhage, infection, hypertensive disorders of pregnancy (preeclampsia, HELLP syndrome, eclampsia), and obstructed labor. One area that NICHD has recently focused on is obstructed labor. Prolonged or obstructed labor can lead to maternal death, fetal death, and obstetric fistula (a hole in tissue in or near the birth canal that results in chronic urine or fecal leakages). Every year, about 100,000 women worldwide develop an obstetric fistula during childbirth, and approximately 2 million women globally are living with fistulae that have not been repaired, many of whom are ostracized by their communities and families. NICHD recently issued a funding opportunity announcement to promote epidemiological, clinical, and behavioral research on obstetric fistulae.

There are several countries that routinely monitor maternal morbidities (Scottish Confidential Audit of Severe Maternal Morbidity 7th Annual Report 2009
[http://www.healthcareimprovementscotland.org/programmes/reproductive, maternal child/pro](http://www.healthcareimprovementscotland.org/programmes/reproductive,_maternal_child/pro)

[gramme_resources/scasmm.aspx](#)). NICHD is exploring the feasibility of holding a scientific workshop to harmonize definitions for these complex conditions in the U.S. In addition, the NICHD staff is working with the Departments of Health and Human Services, and State, on a workshop on maternal mortality that will be held in the Spring of 2012, where it is expected that issues related to maternal morbidity will also be discussed.

Item

Metabolic Bone Disease. - The Committee is encouraged by results thus far from the Bone Mineral Density in Childhood Study, which will serve as a valuable resource for clinicians and investigators to assess bone deficits in children and risk factors for impaired bone health. The Committee urges the Institute to extend the study and explore additional research that will lead to a better understanding and prevention of osteopenia and osteoporosis. (p. 95-96)

Action taken or to be taken

The NICHD-supported Bone Mineral Density in Childhood Study (BMDCS) provided, for the first time, a longitudinal characterization of bone mass accrual in childhood, linear growth, sexual and skeletal maturation, dietary intake, physical activity, and health history. This large, multi-center study included a cohort of multi-ethnic children ranging in age from 5-20 years. The resulting data offered an unprecedented opportunity to identify predictors of the timing and magnitude of peak bone mass, a major determinant of osteoporosis in later adulthood.

Although the study did not follow the cohort until participants reached peak bone mass, it garnered numerous beneficial results. First and most important, the study achieved the primary goal of developing reference data for bone mass and density for children and adolescents. As with the height and weight growth charts currently used by pediatricians, reference curves generated by this carefully executed study will provide the standard for normal bone accrual for generations to come. The BMDCS findings also enable practitioners to identify adverse effects of chronic illness on bone. Finally, the results have elucidated the effects of pubertal timing on bone, the need for height adjustment to analyze “DXA scans” (used to measure bone mineral density), and racial disparities in fracture rates in children. All of these findings enhance our knowledge of maximal bone health, and will continue to be of use as additional research into treatments and diagnostics is pursued.

In addition, NICHD intramural investigators are addressing bone health by studying a severe genetic form of osteoporosis in children, osteogenesis imperfecta (“brittle bone disease”), which affects one in 15-20,000 births. They have shown that deficiency of any one of three proteins—proteins that together form a complex in the cell that modifies collagen in bone and cartilage—can cause osteogenesis imperfecta. One mutation was found to have originated in West Africa, where it is carried by 1.5 percent of the contemporary population. Although osteogenesis imperfecta is a rare condition, these studies continue to reveal important new information about normal bone formation as well.

Item

Preterm Birth. - The Committee notes that the preterm birth rate has begun to decline from its peak of 12.8 percent in 2006 to 12.3 percent in 2008. The Committee urges increased Federal investment to continue the downward trend. Specifically, the Committee urges NICHD to expand its support of prematurity research by creating integrated transdisciplinary research centers on preterm birth as recommended by the Institute of Medicine and the Surgeon General's Conference on the Prevention of Preterm Birth. To initiate this process, the Committee encourages NICHD to establish transdisciplinary research centers for prematurity. The Committee also encourages NICHD to expand its support for preterm birth-related research through the Maternal-Fetal Medicine Units Network, the Neonatal Research Network and the Genomic Proteomic Network for Preterm Birth Research. (p. 96)

Action taken or to be taken

NICHD is strongly committed to reducing prematurity, to understanding its causes, and to identifying interventions for both mothers and babies that will optimize their health outcomes. NICHD has several research networks that take a transdisciplinary approach to addressing prematurity.

Two of the newest NICHD-supported networks incorporate a transdisciplinary approach to understand prematurity and related health concerns more fully. The ongoing “Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (NuMOM2b)” is evaluating the mechanism and prediction of adverse pregnancy outcomes in 10,000 women pregnant for the first time in a prospective cohort study of a racially, ethnically, and geographically diverse populations. The aim of this study is to determine factors in the first and early second trimester that can help identify women at the highest risk for preterm birth, preeclampsia, fetal growth restriction, and stillbirth and, ultimately, to create methods for testing for these conditions. The Prenatal Alcohol and Sudden Infant Death Syndrome and Stillbirth Network conducts community-linked studies to investigate the role of prenatal alcohol exposure in the risk for SIDS and adverse pregnancy outcomes. Its transdisciplinary team includes fetal physiologists, pathologists, developmental biologists, and pathologists, along with clinicians, geneticists, statisticians, and epidemiologists. Most recently, the Network has included sleep experts to evaluate the role of sleep disordered breathing during pregnancy.

Realizing the advances that often are made when a wide range of experts focus on an issue, NICHD brought this transdisciplinary approach to its other, long-standing networks. The Maternal Fetal Medicine Units Network (MFMU) was established to perform clinical trials and conduct studies to improve pregnancy outcomes, with a special emphasis on reducing preterm birth. Several of the studies and trials conducted under the MFMU’s auspices included input from transdisciplinary research groups of basic scientists, pathologists, clinicians, neurodevelopmental specialists, statisticians, epidemiologists, and clinical trialists. One such study, a clinical trial of 10,000 pregnant women that evaluated whether vitamins C and E prevent preeclampsia, utilized collaborative assessments throughout pregnancy, finding that these vitamins (which were being widely prescribed for pregnant women) did not prevent preeclampsia. The Neonatal Research Network was established to conduct observational and interventional studies to improve health outcomes for newborns, and it brings together experts in neurology, developmental pediatrics, genomics, pharmacology, surgery, and ophthalmology to

conduct studies focused on newborn problems such as encephalopathy, bowel problems, blindness, and markers of disease.

The Genomics and Proteomics Network, designed as a transdisciplinary network, brings together experts in genomics and proteomics with clinicians, statisticians, and epidemiologists, to apply advances in genomics and proteomics related to other conditions (such as cardiovascular disease) to the field of prematurity. This group is studying the genetic and environmental etiologies and mechanisms of spontaneous preterm birth with the goal of identifying biomarkers for the increased risk of preterm delivery, and with the ultimate hope of designing effective prevention strategies.

Item

Prosthetics Research. - The Committee is aware that increasing numbers of Americans are undergoing amputation as a result of the growing prevalence of diabetes, cardiovascular disease and other reasons. The Committee also understands that, to date, little research has been done to examine prosthetic outcomes and to link prosthetic and orthotic treatments, devices and supports to patient outcomes. In order to support evidence-based healthcare practice in prosthetics and orthotics, and establish which approaches work best for which patients, the Committee encourages NICHD to work with the National Institute on Disability and Rehabilitation Research and experts in the field of prosthetic research to develop a prosthetics outcomes research agenda and implement needed research. (p. 96)

Action taken or to be taken

NIH agrees that there is a growing need to advance our understanding of the health outcomes for patients requiring prosthetic and orthotic devices and treatments. Two years ago, the NICHD's National Center for Medical Rehabilitation Research (NCMRR), issued a Request for Applications, soliciting grant applications on "Outcomes Research in Orthotics and Prosthetics." The Institute received numerous applications, and recently funded a number of research projects in this area, including an award to the University of Washington to develop a "Client-Based Outcome System for Individuals with Lower Limb Amputation," as well as various academic and small business grants to improve sensory feedback and to prevent potential secondary complications of prosthetics such as infection and ulceration. In addition, NICHD supports a doctoral research program at the Georgia Institute of Technology to train researchers in prosthetics and orthotics.

The director of NCMRR serves on review panels for the Veterans Administration (part of the Department of Veterans Affairs (VA)) and the Department of Defense research efforts in prosthetics and orthotics. The VA is the nation's largest single purchaser of prosthetics and orthotics. The director of NCMRR also serves as the coordinator of rehabilitation research efforts at NIH, and is the NIH representative to the Interagency Committee on Disability and Rehabilitation. The Interagency Committee, which includes the National Institute on Disability and Rehabilitation Research, is in the midst of a strategic planning process. Outcomes measurement for prosthetics and orthotics are included in those discussions.

Item

Psychotropic Drugs and Children. - The Committee is aware that NICHD has formed a special workgroup, which includes representatives from NIMH and the FDA, to better understand the impact of medications on developing children. The Committee requests an update in the fiscal year 2013 congressional budget justification on the workgroup's activities regarding psychotropic drugs and a description of the basic and clinical research the workgroup believes should be undertaken. (p. 96)

Action taken or to be taken

NIH is committed to research aimed at understanding the benefits and risks associated with psychotropic medication use in children. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is charged with implementing the NIH-related provisions of the Best Pharmaceuticals for Children Act (BPCA) and leads a trans-NIH working group to coordinate research efforts on pediatric drug testing (<http://bpca.nichd.nih.gov/collaborativeefforts/index.cfm>). Annually, the BPCA Working Group, in consultation with outside experts, prioritizes drugs or pediatric therapeutic areas in need of pediatric testing. NIH then takes these priorities into consideration when developing related research initiatives. Topics currently on the priority list include: possible adverse consequences of long-term use of antipsychotic medications in children (initial data gathering underway); potential methylphenidate (i.e., Ritalin) toxicity in children (study near completion); and the safety and efficacy of lithium for acute mania in bipolar disorder (study in progress).

To address specific safety concerns associated with commonly prescribed psychotropic medications in childhood, the Working Group has undertaken efforts to understand the biochemical mechanisms underlying adverse effects. While it is recognized that second generation antipsychotics can result in abnormalities such as obesity, diabetes, and hyperlipidemia (elevated cholesterol and fatty substances in the blood), it is not known how these medications change metabolism in order to produce adverse effects. Understanding the mechanism of medication toxicity during childhood is critical to developing safer treatments. In order to address this knowledge gap, NICHD issued a request for applications (RFA-HD-10-010; “Molecular Mechanisms of Adverse Metabolic Drug Effects in Children and Adolescents”) to study the mechanisms of metabolic adverse effects induced by medications in children.

Another project stemming from the BPCA Working Group that was recently completed through an interagency agreement between NICHD, the Food and Drug Administration, and the National Institute of Mental Health addressed the effects of long-term administration of the stimulant medication methylphenidate (i.e., Ritalin) on pubertal development. Stimulants are the most commonly used psychotropic medication in children and adolescents, and treatment can last years, including during puberty. The study, conducted in laboratory animals, showed that medication had a time-limited effect in delaying the testosterone increase that is typically seen in early puberty. Further investigation of the biochemical changes that psychotropic medications may induce in children and adolescents will provide clues to preventing or counteracting adverse effects.

Item

Rehabilitation Research. - The Committee commends NIH for appointing a blue-ribbon panel to evaluate rehabilitation research at the National Center for Medical Rehabilitation Research [NCMRR] and across all of NIH. The Committee requests a copy of the panel's report when it is available. The panel is urged to identify gaps in the field of rehabilitation research and recommend which ICs or other Federal agencies should be responsible for addressing them. In addition, the Committee recognizes the improvements that have been made in delineating rehabilitation research as part of NIH reporting mechanisms established since the passage of the NIH Reform Act. However, the Committee encourages NIH, through the leadership of NCMRR, to further clarify a consistent definition of rehabilitation across all institutes and centers and to seek ways to delineate between physical, cognitive, mental and substance abuse rehabilitation when characterizing NIH-supported research. Finally, the Committee encourages NCMRR to explore the broader social, emotional and behavioral context of rehabilitation, including effective interventions to increase social participation and re-integrate individuals with disabilities into their communities. (p. 96-97)

Action taken or to be taken

Within NIH, the NICHD's National Center for Medical Rehabilitation Research (NCMRR) supports research on enhancing the health, productivity, independence, and quality-of-life of people with physical disabilities. In addition, NCMRR chairs the trans-NIH Rehabilitation Coordinating Committee whose members include representatives from NIH Institutes and Centers that support rehabilitation research.

A Blue Ribbon Panel on Rehabilitation Research was established in 2011 to assess rehabilitation research across NIH. The panel is co-chaired by a member of the National Advisory Child Health and Human Development Council and by a member of the NCMRR Advisory Board. Thirteen scientists were named to the Panel, representing a wide range of expertise including rehabilitation sciences, bioengineering, and physiology. The Panel met in October 2011 to discuss the nomenclature associated with "medical rehabilitation", to review the history of NCMRR, current rehabilitation research at NIH, and the recent Institute of Medicine report, *Disability in America*. The Panel plans to meet again in early 2012. NCMRR staff has worked extensively with staff from the Office of the NIH Director to define the parameters of rehabilitation research at NIH to ensure uniform reporting across the organization. This will be an ongoing effort as the Blue Ribbon Panel clarifies the definition of rehabilitation research at NIH. In turn, increasing precision in the definition will allow further refinement of the "fingerprint" produced by the Research Condition and Disease Categorization (RCDC) database.

Current research supported by NCMRR includes grants that address community participation by individuals with disabilities, health disparities faced by those with disabilities, family, school, and community support, and strategies to promote participation in a full range of employment, education, social, and recreational opportunities. Recently, the NCMRR issued trans-NIH Funding Opportunity Announcements on "Health Promotion for Children with Physical Disabilities through Physical Activity and Diet: Developing an Evidence Base," and "Design and Development of Novel Technologies for Healthy Independent Living."

Item

SMA Newborn Screening. - The Committee applauds NICHD for funding a pilot study of newborn screening for spinal muscular atrophy [SMA] that will confirm the efficacy and accuracy of the SMA screening technology. The Committee understands that new born screening holds promise for assisting with early interventions of SMA and developing improved and more standardized care protocols for patients living with SMA, and it may also assist in the development of potential drug therapies. Natural history, pre-clinical and preliminary clinical data all suggest that potential therapies will demonstrate the greatest effectiveness when delivered pre-symptomatically. The Committee encourages NICHD to support the development of crucial follow-up care protocols for children identified with SMA through the pilot study, and to report on progress made in this area in the fiscal year 2013 budget justification. (p. 97)

Action taken or to be taken

Spinal muscular atrophy (SMA) is the most common inherited motor neuron disease in humans, with an incidence of approximately one in 8,000 live births. It is a leading cause of hereditary infant and childhood mortality. Identifying newborns with SMA and defining the sequence and timing of the onset of symptoms and complications of the disease would assist in understanding the genetic and clinical differences in the presentation of the disorder and could potentially assist in prevention, management, and treatment of SMA symptoms and complications.

Under a contract awarded by NICHD, research is underway to develop and validate a newborn screening test for SMA. The test is based on detecting the deletion of the SMN1 gene, which is common among patients with SMA, and it will be initially tested within the investigator's laboratory using blood samples from these patients. If proven successful, pilot studies will be conducted at a public health newborn screening laboratory to demonstrate the viability of screening for SMA on a larger scale.

NICHD also is funding a multi-faceted natural history study on different aspects of newborn screening for SMA. Researchers are exploring the ethical, regulatory, and policy issues related to the use of public health newborn screening programs for SMA. This information will allow the investigators to develop educational materials for parents, key stakeholders, and researchers. Through the pilot newborn screening program, the research team also will implement and assess the impact of a multidisciplinary approach to early diagnosis and management on health outcomes (using standardized outcome measures) in infants and children identified with SMA by creating a subspecialty-based medical home for identified infants and their families.

Both of these newborn screening projects are leveraging infrastructure support from the Newborn Screening Translational Research Network (NBSTRN). The NBSTRN is a resource created by NICHD to provide researchers in the area of newborn screening with a network of support services and centralized infrastructure to facilitate the capture and storage of longitudinal clinical data from individuals identified with a disorder via newborn screening.

Item

Vulvodynia. - The Committee is encouraged by positive signs that NICHD is devoting greater attention to this long-neglected condition, especially with regard to stimulating interest in both the intramural and extramural research community and ensuring adequate representation of vulvodynia experts on peer-review panels. The Committee expects to be updated on progress in these areas in the fiscal year 2013 congressional budget justification. The Committee also notes that vulvodynia often coexists with other persistent pain conditions, including interstitial cystitis, fibromyalgia, temporomandibular joint and muscles disorders, irritable bowel syndrome, endometriosis, headache, and chronic fatigue syndrome. The Committee strongly urges the creation of a trans-NIH research initiative that will support studies aimed at identifying common etiological pathways among these disorders, with the goal of developing potential therapeutic targets. (p. 97)

Action taken or to be taken

Researchers have estimated that 9 to 18 percent of women between the ages of 18 and 64 experience vulvar pain during their lifetimes, but no cure or reliable treatment exists for vulvodynia and related chronic pain conditions.

In July 2011, NICHD sponsored a scientific meeting, *Vulvodynia: A Chronic Pain Condition – Setting a Research Agenda*. The meeting brought together a diverse group, including more than 80 scientists from NIH, the pharmaceutical industry, and academic medicine, as well as patients and clinical practitioners. Participants discussed the need for additional research capacity in fields related to vulvodynia, the relationship between vulvodynia and other chronic pain conditions, and specific research gaps to be addressed, such as the causes of vulvodynia, what factors may trigger these disorders, and how to prevent or treat vulvodynia's symptoms. NICHD is drafting a research plan aimed at enhancing capacity for research on vulvodynia and identifying key areas that need to be addressed to move the research forward. The draft plan was posted for public comment at the end of 2011, and NICHD expects to publish the final plan in early 2012.

In addition, NICHD continues to solicit grant applications through three ongoing funding opportunity announcements on systematic, epidemiologic, or therapeutic studies related to vulvodynia. Following a Technical Assistance webinar to aid potential applicants in submitting competitive proposals, several applications have been received and will be evaluated by a special panel with the requisite expertise to review those applications. Further, NICHD recently funded its first randomized clinical trial on a potential treatment for vulvar pain.

NICHD also is participating in a new trans-NIH working group on overlapping chronic pain conditions, led by NINDS and comprising 13 NIH Institutes and Centers involved in pain research, including vulvodynia. Early plans for the working group include coordinating NIH-supported research on an ongoing basis and planning a trans-NIH conference to summarize current knowledge on overlapping chronic pain conditions and to identify research gaps.

National Eye Institute (NEI)

Senate Significant Items

Item

Age-Related Macular Degeneration [AMD]. - The Committee commends NEI for conducting the Comparison of AMD Treatments Trial, a comparative effectiveness trial of the two leading antiangiogenic drug therapies currently used to treat the "wet" form of AMD. (p. 97)

Action taken or to be taken

In May 2011 the *New England Journal of Medicine* published the much anticipated first-year results of the two-year Complications of AMD Treatments Trails (CATT). CATT investigators found that Avastin and Lucentis are equally effective in treating the advanced, wet form of AMD. More than 250,000 patients are treated each year for this form of AMD, and the majority receives Avastin. Given the lack of efficacy data regarding Avastin for AMD treatment, NEI had an obligation to patients and clinicians to conduct this study.

Avastin was developed by Genentech to prevent blood vessel growth in metastatic colon cancer. Genentech later chemically modified Avastin to create Lucentis, a drug for treating the damaging blood vessel growth in AMD. After publication of very positive results from Lucentis clinical trials, ophthalmologists began using Avastin off-label, as Lucentis had not yet come on the market. Avastin remained in widespread use even after Lucentis was FDA approved.

CATT is a prime example of the value of comparative effectiveness research. Given that the two drugs were developed by the same pharmaceutical company, there was little commercial incentive to evaluate the drugs head-to-head. NEI was the only entity with the expertise and resources to conduct a large-scale trial. With CATT results, doctors and patients can have confidence in the efficacy of both treatment options for this common, sight-threatening disease.

Two-year results from CATT will be published in the spring of 2012. These results will provide longer follow-up data for both safety and efficacy.

Item

Diabetic Eye Disease. - The Committee acknowledges the NEI Diabetic Retinopathy Clinical Research Network's results that laser treatment for diabetic macular edema, when combined with antiangiogenic drug treatment, is more effective than laser treatment alone, and notes that this finding will revolutionize the standard of care that has been in place for the past 25 years. With NIDDK leading a new NIH strategic plan to combat diabetes, NEI's research through its various diabetic eye disease networks will be more important than ever. (p. 97-98)

Action taken or to be taken

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network of investigators and ophthalmologists dedicated to facilitating multicenter clinical research of diabetic retinopathy, diabetic macular edema, and associated conditions. DRCR.net supports the identification, design, and implementation of multicenter clinical research initiatives focused on

diabetes-induced retinal disorders. DRCR.net was formed in September 2002 and currently includes over 109 participating academic and community clinics with over 320 physicians throughout the United States.

With its large network, DRCR.net enables NEI to more rapidly implement protocols and recruit patients for large-scale clinical trials. The development of antiangiogenic drugs, initially for age-related macular degeneration, allowed DRCR.net to quickly evaluate their use in diabetic macular edema. The landmark finding for Lucentis in the treatment of diabetic macular edema spurred DRCR.net to launch new clinical trials evaluating antiangiogenic agents in other forms of diabetic eye disease where the retinal vasculature also becomes compromised.

One protocol, launched shortly after positive results of the diabetic macular edema study were published, is evaluating Lucentis in proliferative diabetic retinopathy (PDR), a more advanced form of diabetic eye disease where fragile blood vessels grow into the retina. PDR can cause severe scarring of the retina and retinal detachment and can lead to rapid, irreversible vision loss. In some cases, the vessels hemorrhage into the vitreous, the clear gel that fills the eye. In such cases, the blood does not always resolve, requiring the patient to have surgery to remove the compromised vitreous. A second trial, set to begin recruiting patients in late 2011, will compare Lucentis to laser treatment in PDR where vitreous hemorrhage is not present.

DRCR.net is actively pursuing identification and design of important clinical trials that complement each other in terms of patient eligibility and therapeutic approach. With a large pool of patients manifesting different forms of diabetic eye disease, DRCR.net is a vital resource for clinical evaluation of new therapies and for comparing the effectiveness of existing therapies.

Item

Genetic Basis of Eye Disease. - The Committee commends NEI for elucidating the genetic basis of devastating eye diseases, such as AMD, retinitis pigmentosa and glaucoma. The Committee is pleased that, building upon the first successful use of genome-wide association studies [GWAS] to determine the increased risk of developing AMD from gene variants, NEI has created a new International AMD Genetics Consortium to bring together researchers to share and analyze GWAS results to further determine the genetic basis of the disease. (p. 98)

Action taken or to be taken

The International AMD Genetics Consortium was created by NEI to identify the remaining risk variants for age-related macular degeneration (AMD). The consortium brings together 15 GWASs from around the world representing over 8,000 cases with AMD and 50,000 controls. Consolidating these data sets provides a highly powered sample size to conduct meta-analysis studies to confirm previously reported gene variants, identify new variants of significance, and suggest less common variants that may require further study to validate.

Thus far, the consortium has validated eight gene variants that were identified in previous GWAS studies. It has also identified DNA variants in 19 additional genes. The genes identified in these studies function in the immune system, cholesterol transport and metabolism, and connective tissue. Identification of the biologic pathways where these genes function has greatly

increased the understanding of this complex disease and allows researchers to further pinpoint the underlying mechanisms of the disease.

As a complement to findings from the AMD Genetics Consortium, NEI recently funded a grant to discover and validate rare (less than 1% frequency) and/or moderate (1 to 5% frequency) genetic variants. This study will provide a nearly complete genetic heritability picture for AMD.

The quest to complete the genetic heritability of AMD would not have been possible without the exhaustive efforts of NEI staff to unite the international research community to share GWAS data sets and collaborate to solve a common goal in our understanding of this blinding disease.

Item

Translational Research. - The Committee commends NEI's translational research initiatives through partnerships with other ICs, other agencies within HHS, and private funding organizations. The Committee acknowledges NEI's leadership of the human gene therapy clinical trial for neurodegenerative eye disease Leber Congenital Amaurosis, which has indicated that the treatment is safe and produces lasting visual improvement, and it is pleased that NEI is expanding the trial to younger patients with less severe disease. (p. 98)

Action taken or to be taken

In September 2011, NEI-supported investigators published interim results from 15 patients treated with gene transfer for Leber congenital amaurosis. Based on encouraging results in 2008, the research group endeavored to improve the technique by evaluating several variables, including increasing the viral vector dose by administering two subretinal injections in different areas of the retina, injecting vector beneath the photoreceptor-rich area of the retina called the fovea, and treating younger patients with presumably healthier retinas.

To date, all 15 participants experienced modest visual improvements with no complications, including the original three patients who were treated three years ago. Administering an additional injection safely expanded the amount of retina exposed to treatment. Photoreceptor cells near injection sites had measurable increases in sensitivity when compared to baseline measures before treatment.

The scientists were unable to demonstrate that injecting vector subfoveally improved outcome, compared to injecting vector into other parts of the retina. When measured with optical coherence tomography, a noninvasive technique used to examine the retina, some participants who received subfoveal injections experienced foveal thinning, which suggested a loss of photoreceptors.

Younger participants, compared to older participants, did not experience greater visual improvements. In fact, the two patients with the greatest visual acuity gains were among the oldest in the study. The researchers speculate that the number and health of remaining photoreceptors matter more than patient age, as the rate of photoreceptor loss varies considerably among people with LCA. This finding suggests that older patients with slower photoreceptor degeneration may be good candidates for the therapy.

Because safety was the primary outcome of this trial, a conservative approach was taken that limited treatment to the eye with poorer vision. With safety established, further research will be carried out to determine whether additional visual gains are possible by treating patients' better eye.

National Institute of Environmental Health Sciences (NIEHS)

Senate Significant Items

Item

Multidisciplinary Research. - The Committee notes that research conducted through NIEHS is steadily revealing previously unrecognized influences of environmental exposures on a wide range of diseases and conditions, including breast cancer, autism, obesity, asthma and chemical sensitivities, and has the potential to lead to novel methods of preventing, detecting and treating disease. The Committee commends NIEHS for its research across many disease areas, including the Institute's translational and community-based studies, and involving those living in rural communities. (p. 98)

Action taken or to be taken

NIEHS has made remarkable achievements in linking health outcomes with environmental influences by recognizing and studying unexplored pathways of environmental effect by using new and old tools from biology, chemistry, toxicology, genetics, and many other disciplines. A new NIEHS study found that children with autism are far more likely to have deficits in mitochondrial function, specifically in their ability to produce cellular energy, than typically developing children. The results indicate that cumulative damage and oxidative stress in mitochondria could influence both the onset and severity of autism.

Liver cancer (hepatocellular carcinoma) is promoted by a chronic inflammatory state that coincides with obesity. Liver cancer development was dependent on two well known inflammatory factors, IL-6 and tumor necrosis factor. NIEHS-supported research helped to show that the absence or suppression of receptors for either of the two cytokines reduced the incidence of this form of liver cancer in laboratory mice.

A community-university partnership used community-based participatory research to design, implement, and evaluate a multi-cultural public health campaign to eliminate flammable products and reduce use of products high in volatile organic compounds in hardwood. Outreach led by community partners reached a large proportion of floor finishers, was associated with use of safer products, and added to recent work on community-based participatory research with immigrant workers.

Scientists have discovered the seventh and eighth bases of DNA thought to play a role in removing a methyl group (CH₃) from DNA and stem cell reprogramming. The findings have important implications for stem cell research since they provide researchers with new tools to erase previous epigenetic methylation patterns and to reprogram adult cells. This could give scientists the opportunity to reactivate tumor suppressor genes that had been silenced inappropriately by DNA methylation. The importance of epigenetic processes is being confirmed with increasing frequency. An NIEHS-funded study has reported that breast tumor size is associated with tumor DNA methylation profile.

Linked resources like the Environmental Polymorphism Registry, a collaborative 20,000 patient registry being used by researchers at NIEHS and the University of North Carolina at Chapel Hill,

facilitate genotype-driven translational research of environmental disease and help scientists identify populations at risk and develop strategies for preventing and treating disease. Translational research of complex disease involves identifying underlying susceptibility loci and the environmental factors that affect development and/or progression of disease, and applying this information to clinical strategies for predicting, preventing, diagnosing, and/or treating disease.

Item

Public Health Hazards. - The Committee recommends that NIEHS address the public health hazards associated with exposure to volcanoes, such as on the Big Island of Hawaii, and continue efforts to evaluate the health impact of natural environmental hazards. (p. 98)

Action taken or to be taken

NIEHS agrees that the health hazards associated with exposure to volcanic eruptions and other natural environmental hazards are important public health concerns. NIEHS-funded researchers have shown that there is a strong relationship between volcanic ash exposure and respiratory effects in children. The absence of real-time exposure data and the time required to reach and evaluate patients during an emergency are complicating factors in assessing the effects of volcanic eruptions such as on the Big Island of Hawaii. NIEHS-supported researchers are developing a field-deployable system that can be used in large population studies to measure participants' physiological responses to particulate matter or other environmental stressors that can occur in volcanic eruptions.

NIEHS is also conducting research on another environmental health hazard that is of concern in Hawaii - contamination of coastal beaches, the primary sites used for recreational activities. Although sewage is not routinely discharged into coastal waters, fecal bacteria from land-based discharges from streams and storm drains can flow into coastal waters. Evaluation of recreational water quality is frequently based on the level of fecal-related bacteria, such as coliform and enterococci. However, such tests may not detect the presence of waterborne viral pathogens or viruses that infect bacteria and, indeed, previous studies have confirmed that tests for enterococci and *Escherichia coli* (*E. coli*) are unreliable indicators of fecal water contamination in Hawaii.

NIEHS research has led to the development of two new assays that detect viral pathogens and can be used as an index for recreational water quality in Hawaii. The first assay tests for human adenovirus as an index of human waste pollution. Using three polymerase chain reaction (PCR) protocols, NIEHS-supported scientists were able to detect human adenoviruses in treated and untreated urban wastewaters and recreational water samples collected around the island of Oahu, Hawaii. Findings from this study support the use of PCR testing for the presence of enteric viruses as an effective means of monitoring the aquatic environment of Hawaiian beach waters. The second assay builds on findings from public health efforts in other areas that successfully measured the presence of viruses that infect bacteria in water using a geographically specific host bacterium. By isolating a host (HB 73) specific for use in Hawaii, NIEHS-supported scientists were able to recover viruses from multiple sources of raw sewage samples produced on the island of Oahu. The HB 73 method promises to be a more sensitive method for detection of

sewage contamination in the waters in Hawaii. These advances may help protect Hawaii's public health in the State's recreational waters.

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National Institute on Aging (NIA)

Senate Significant Items

Item

Age-Related Bone Loss. - The Committee supports the Institute's continuing Biology of Aging Program and appreciates the focus on developing a further understanding of aging processes, health and longevity. Given the demographics of our rapidly aging population, a continuing need exists for new therapeutic approaches to prevent and treat age-related bone loss, fractures and other metabolic bone diseases, including osteogenesis imperfecta, glucocorticoid-induced osteoporosis and bone loss due to kidney disease. (p. 99)

Action taken or to be taken

NIA's Division of Aging Biology continues to support a robust program of research on the basic biochemical, genetic, and physiological mechanisms underlying the process of aging in humans and animal models in collaboration with NIAMS and other NIH institutes and centers. New initiatives to explore the basic biology of aging from a systems perspective – i.e., by investigating the complex interactions at the single-cell level among individual gene products, biochemical pathways and cell biological mechanisms that impact aging, as well as interactions between tissues – and to elucidate the effects of aging began in 2011 and will continue to be active in FY 2013.

NIH also supports a broad range of basic research on bone and is using these findings to identify new therapeutic approaches to the prevention of age-related bone loss. For example:

- Recent basic research findings indicate that regulation of bone mass is highly complex, involving not just the bones themselves but also a “central relay” involving the serotonin system in the brain. In FY 2010, NIA issued a research solicitation for applications to study the etiology and/or mechanisms regulating bone mass that are regulated by a central relay. The resulting studies will significantly enhance our understanding of the integrated nature of the age-related changes in bone mass, and we anticipate that they will suggest novel therapeutic targets to prevent bone loss in older women and men. Studies will be active in FY 2013.
- There is a growing recognition that common health problems such as diabetes, heart disease, and osteoporosis are not independent phenomena. The processes that underlie these conditions interact, and NIH supports studies to identify and characterize age-related changes in factors that integrate activity influencing bone mass, as well as the various mechanisms that coordinate these signaling pathways.
- The exciting observation that bone also has a role as an endocrine organ, regulating activities in other organs, has opened a new avenue of research aimed at understanding the integration of body composition and energy balance. Ongoing studies into the mechanisms of action of these novel endocrine regulators are designed to uncover their roles in disease and provide insight into the development of novel therapeutic treatments.
- With respect to conditions that predispose people to compromised bone strength, including chronic kidney disease, NIH supports research to understand the mechanisms

involved and to develop non-invasive detection methods to monitor bone health as well as treatment response.

- The Study of Osteoporotic Fractures (SOF) in women and the Osteoporotic Fractures in Men study (MrOS) continue to provide a wealth of information about risk factors for osteoporotic fractures. Findings from these observational studies may ultimately be used to generate hypotheses about therapeutic targets. Both studies will be active during FY 2013.
- Longitudinal studies such as the Study of Women's Health across the Nation (SWAN), the Rancho Bernardo Study, and the Framingham Study explore an array of age-related health conditions, including osteoporosis.

Item

Basic Behavioral Research. - The Committee applauds the Institute's leadership role in the OppNet initiative, which will build a collective body of knowledge about the nature of behavioral systems, deepen the understanding of basic mechanisms of behavioral processes and emphasize the relevance of basic behavioral science research throughout NIH's mission. (p. 99)

Action taken or to be taken

OppNet, NIH's Opportunity Network for Basic Behavioral and Social Science research (b-BSSR) grants, is a trans-NIH initiative that was established in November 2009 to expand NIH's portfolio in b-BSSR, scientific inquiry that explains the mechanisms and processes that influence individual and group health-related behaviors. OppNet's mission is to pursue opportunities for strengthening basic behavioral and social science research at NIH while innovating beyond existing investments.

All NIH Institutes and Centers (ICs) that fund extramural research collectively fund and manage OppNet. Twenty-four ICs and five program coordination offices within the NIH Office of the Director integrate existing NIH efforts, target research challenges best met collectively, and collaborate on new research initiatives in complementary scientific areas. OppNet also receives vital input from its stakeholders, who have provided scientific perspectives through a Request for Information in January-February 2010 and a public conference in October 2010.

As of July 2011, OppNet supported 73 extramural research projects totaling over \$14 million under 18 separate research solicitations. Research topics were diverse and included self-regulation across the lifespan, the effects of the social environment on health, the interaction of sleep and behavior, and the development of new and comprehensive measures of psychosocial stress that can be applied across species and across the lifespan. Many of these projects will continue to be active during FY 2013. A new research solicitation on the basic cognitive, affective, motivational, and social processes that underlie decision making across the lifespan was recently released; it is anticipated that 5 to 15 grant awards will be made, and these projects will be active during FY 2013.

NIA has appreciated the opportunity to play a leadership role in OppNet and looks forward to continuing that role in the future. NIA Director Richard J. Hodes is a co-chair of the OppNet

steering committee, and several NIA program staff members, primarily from the Division of Behavioral and Social Research, have led the development of OppNet research solicitations.

Item

Demographic and Economic Research. - The Committee commends NIA for prioritizing support of the Health and Retirement Study [HRS], which includes data from a representative sample of 20,000 Americans aged 50 and over regarding their health and healthcare needs, income and savings, and work and retirement plans. NIA is especially encouraged to continue its successful collaboration and co-funding agreements for the HRS with the Social Security Administration. The Committee commends NIA's initiative in developing comparable international surveys, particularly in countries that have aged faster than the United States. The Committee anticipates important research advances regarding gene-environment interactions once the genome-wide array study of the HRS sample is fully implemented. (p. 99)

Action taken or to be taken

NIH anticipates renewing funding in FY 2012 for the Health and Retirement Study (HRS), which consists of a biennial collection of data from nationally representative, population-based sample of over 22,000 Americans aged 50+ and their spouses. 10 waves of data have been collected to date (1992-2010). The study has been enormously productive; over 1700 scientific publications have resulted from the HRS, and the number of registered users of HRS data continues to increase. HRS data continue to be an important resource for researchers, students, and other government agencies.

NIA receives significant co-funding for the study (currently around 22%) from the Social Security Administration (SSA), and we anticipate that this fruitful collaboration will continue. SSA grantees and other researchers working on retirement savings and pensions use HRS data extensively.

Importantly, the HRS is a model for similar studies around the world. NIA has taken the lead in building the necessary infrastructure and harmonizing cross-national data resources to facilitate comparative studies and has funded the initial concept work for HRS-like studies in other countries. Today, similar studies are ongoing in England, China, South Korea, Mexico, and Japan and on the European continent. Other studies, notably the World Health Organization's Study on Global Health and Ageing and Adult Health (which includes sites in Asia, Russia Mexico, and Africa), have adapted methods and/or instruments from the HRS for their own use. Population aging is occurring even more rapidly than the United States in many of these regions, particularly in the developing world, which is projected to see a 140% increase in the 65-and-older population by 2030. In addition, NIA has supported the development of an on-line resource that facilitates use and harmonization of data from the HRS and comparable studies around the world.

Support from the American Reinvestment and Recovery Act has enabled the HRS to conduct genotyping on approximately 20,000 participants. NIH has recently begun soliciting research projects that will use this newly available genetic data to advance our understanding of how genetic, behavioral, and psychosocial factors affect the health and well-being of older

Americans. We anticipate that these projects will begin next summer and will be active through FY 2013.

Item

Life Course Perspectives. - The Committee encourages NIA to maintain its important emphasis on life course studies, which focus on how transitions among family and other relationships may affect health, healthcare and aging. (p. 99)

Action taken or to be taken

NIA continues to support several major initiatives that focus on the transitions among family and other relationships and the effects of those transitions on health, healthcare, and aging.

- The **Health and Retirement Study (HRS)** explores physical and mental health, insurance coverage, living situations, economic circumstances, family support systems, work status, and retirement planning among Americans aged 50 and older.
- The **Panel Study on Income Dynamics (PSID)** is a longitudinal study of a representative sample of U.S. individuals and the families. It emphasizes the dynamic aspects of family economics, demography, and health. Data have been collected since 1968, making the PSID the longest running panel on family and individual dynamics. These data are being used to support increasingly complex models of outcomes for individuals over the life cycle, for relatives within the same generation of a given family, and for individuals across multiple generations of the same family. These models facilitate the use of innovative research strategies to yield a greater scientific understanding of ways to promote individual health and well-being. NIA co-funds the PSID with the National Science Foundation, the Eunice Kennedy Shriver National Institute on Child Health and Human Development, and several other private and governmental partners.
- The **Wisconsin Longitudinal Study (WLS)** is a long-term study of 10,317 men and women who graduated from Wisconsin high schools in 1957. WLS investigators are studying a wide array of social, behavioral, and economic parameters among participants, and are currently conducting a new wave of interviews.
- Since its establishment in 1958, the NIA's **Baltimore Longitudinal Study of Aging (BLSA)** has provided a wealth of information on the physical consequences of aging and has helped distinguish changes due to aging from those due to disease, genetic makeup, environmental or lifestyle factors, or other causes. Many of the active participants have been in the study for more than 20 years, and some for as long as 44 years. Recently, NIA initiated the Insight into the Determinants of Exceptional Aging and Longevity (IDEAL) substudy to examine a spectrum of characteristics found in individuals over age 80 who are living free of physical or cognitive disease. The IDEAL study will help uncover mechanisms – including behavioral, lifestyle, and environmental factors -- that are important to exceptional aging and how they might translate into actions that promote health and physical function in older adults.
- The **National Health and Aging Trends Study (NHATS)**, a successor to the National Long-term Care Study, is in its first wave of data collection. It will provide a greatly improved ability to track and explain trends in disability and the social and economic impact of late-life functional changes for older people, their families, and society.

- **The ongoing Healthy Aging in Neighborhoods of Diversity Across the Lifespan (HANDLS)** study is examining the clinical, behavioral, and psychosocial characteristics across the life course among African American and white residents of Baltimore.

NIA also supports a number of smaller studies exploring aspects of health and well-being across the life course. Notably, in FY 2011, NIA issued a solicitation for research grant applications that will expand our understanding of the effects of family and interpersonal relationships on behavioral and social processes of relevance to aging, and on how these processes change over the life course and across cohorts. Studies will be active in FY 2013.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Senate Significant Items

Item

Marfan Syndrome. - The Committee encourages NIAMS to expand support for research on the multi-body system disorder Marfan syndrome, including musculoskeletal and extracellular matrix biology studies. (p. 99)

Action taken or to be taken

Marfan syndrome is a heritable condition that affects the extracellular matrix that serves as connective tissue in holding the body together and providing a framework for growth and development. In Marfan syndrome, the connective tissue that is found throughout the body is abnormal and does not act as it should, adversely affecting many body systems, including the skeleton, eyes, heart and blood vessels, nervous system, skin, and lungs and, in some cases lead to complications that are life threatening. Because Marfan syndrome affects the long bones of the skeleton, a person's arms, legs, fingers, and toes may be disproportionately long in relation to the rest of the body. Other skeletal problems include a sternum (breastbone) that is either protruding or indented, curvature of the spine (scoliosis), and flat feet.

Several years ago, NIH-funded researchers found that losartan, a common blood pressure medication, also affected a molecular pathway involved in aortic weakening and rupture, an often fatal complication of Marfan syndrome. Building on this research, recent NIAMS-supported research is shedding light on the molecular mechanisms of losartan's effects on controlling the development of these defects, called aortic aneurysms. In another recent discovery, scientists funded by NIAMS found a key regulator of connective tissue structures that may contribute to their malfunction in Marfan syndrome. This new knowledge furthers our understanding of the molecular pathogenesis in Marfan syndrome, and reveals potential new drug targets for treatment.

NIAMS continues to support a broad portfolio of connective tissue biology and musculoskeletal research that is relevant to Marfan syndrome. Advances in these programs could help to inform the field of Marfan research and, ultimately, improve the quality of life of patients. NIAMS encourages Marfan investigators to engage colleagues within the fields of musculoskeletal and connective tissue biology in order to explore new areas of research and collaboration focused on the musculoskeletal manifestations of the disease.

Item

Scleroderma. - The Committee continues to prioritize research on scleroderma and commends the Institute for its ongoing efforts in this area. The Committee notes the high mortality associated with pulmonary complications from scleroderma, and it encourages NIAMS to collaborate with NHLBI on this important issue. (p. 99)

Action taken or to be taken

Scleroderma is a complex group of diseases involving abnormal growth of connective tissue. It is often manifested as hard, tight skin, but in some individuals, systemic sclerosis (SSc), a form of scleroderma, may affect blood vessels and internal organs, such as the heart, lungs, and kidneys. Scleroderma is believed to be an autoimmune disease, in which the immune system attacks the body's own tissues.

Pulmonary complications, including pulmonary fibrosis (PF) and pulmonary arterial hypertension (PAH), are the leading cause of mortality in patients with SSc. Current therapies for SSc lung disease have shown only modest benefit, with patients often requiring lung transplantation. A study supported by NIAMS compared lung tissue of SSc patients who had these complications with tissue from healthy patients, and those who had PF and PAH unrelated to SSc. Analysis of these tissues revealed specific genes that were differently expressed in the SSc patients, as compared with those without SSc. In a separate study, investigators at the NHLBI Specialized Center of Clinically Oriented Research (SCCOR) have identified alterations in several cardiovascular disease risk genes that are significantly associated with the development of PAH in scleroderma. They have also found novel clinical hallmarks of disease severity that can predict mortality in patients with scleroderma-associated PAH. These discoveries provide novel insights into the mechanisms of SSc lung disease, and present new directions for collaborative research with NIAMS, including the development of more effective therapies for treatment.

Blood vessel disease is another manifestation of SSc, resulting in the destruction of the small vessels and capillaries, and contributing to complications such as scleroderma renal crisis and PAH. Based on recent research, NIAMS researchers have now confirmed that large blood vessels of the neck, upper arm, lower leg, heart, brain, and kidney are subject to atherosclerosis, or thickening of artery walls, as well. Furthermore, this atherosclerosis was worse in patients with SSc than in patients without the disease, which expands our understanding of the disease, and provides opportunities for developing new treatments.

The Scleroderma Lung Study, a collaboration between NHLBI and NIAMS, is a multicenter clinical trial that found that, despite its initial effectiveness, oral cyclophosphamide was associated with significant toxicity, and that the beneficial effects appeared to diminish one year after termination of therapy. NHLBI is supporting a follow-up scleroderma lung trial evaluating the efficacy of mycophenolate mofetil, an immunosuppressive drug approved for organ transplantation, in comparison with cyclophosphamide. The trial is expected to complete enrollment by the end of 2012.

NIAMS recently funded a new five-year Center of Research Translation (CORT) focused on the pathogenic mechanisms of SSc. CORTs encompass a multidisciplinary approach and are made up of at least one basic and one clinical project. CORT will focus on identifying the biomarkers associated with the complications and progression of scleroderma, setting the stage for more targeted therapies for at-risk individuals. In addition, a newly funded NIAMS-supported Rheumatic Diseases Research Core Center (RDCC) will establish a consortium of investigators that utilize common resources in order to perform high technology analyses of skin and lung

specimens from SSc patients. This data will allow rapid molecular evaluation of potential therapeutic targets.

Item

Temporomandibular Joint [TMJ] Disorders. - Many people who have TMJ disorders suffer from conditions that routinely affect other joints in the body, such as trauma and arthritis. Therefore, the Committee calls on NIAMS to collaborate with NIDCR to study the jaw anatomy and physiology and the complex neural, endocrine and immune system interactions that orchestrate jaw function and trigger jaw joint pathology. NIAMS should integrate findings from studies of the structure, mechanical function, metabolism and blood flow of bone, joints and muscles with studies of central and peripheral neural pathways, as well as the endocrine, paracrine and cytokine factors that impact upon craniofacial structures as a means to understanding the underlying causes of pain and dysfunction. The Committee also urges NIAMS to support comparative studies of the TMJ with other joints that could document similarities and differences at the clinical and molecular levels. (p. 99-100)

Action taken or to be taken

Temporomandibular joint disorders (TMJDs) are a group of conditions that cause pain and dysfunction in the jaw joint and muscles that control jaw movement. NIAMS supports many projects related to joint physiology and disease, which could help to inform the TMJD community. For example, NIAMS-funded researchers studying a class of molecules known as microRNAs recently reported that some of the microRNA sequences that are involved in the production of cartilage also reduce the amount of inflammatory signals that are released by cells in the synovium – a thin membrane that produces fluid to lubricate joints, as well as lowered concentrations of pain-related molecules in the brain and spinal cord.

Following the completion of a study on the molecular basis of inflammatory knee arthritis, NIAMS is supporting a new effort that will apply what was learned to TMJD. The work is funded through the Pathway to Independence program, which supports promising early-stage scientists as they transition from mentored postdoctoral positions to tenure-track, independent research careers. The project will fund new investigators and will center on the development of an animal model of knee arthritis that can be adapted for studies of TMJD sequelae, such as orofacial sensitivity, bite force, dietary habits, and sleep patterns.

The newly appointed Director of the National Institute of Dental and Craniofacial Research (NIDCR), Dr. Martha Somerman, is also heading the new NIAMS intramural Laboratory of Oral Connective Tissue and Biology, which focuses on defining the key regulators controlling development, maintenance, and regeneration of oral-dental-craniofacial tissues. Dr. Somerman and her research team will complement the expertise of existing NIAMS intramural laboratories and provide new opportunities for strategic collaborations to advance knowledge of the physiology of the jaw and other joints.

NIAMS and NIDCR, in association with the NIH Office of the Director, supported the Tenth International Conference on the Chemistry and Biology of Mineralized Tissue. This meeting was held in November 2010 to improve the oral, dental, craniofacial, and bone health of our nation

by encouraging high quality research, facilitating interactions and collaborations by scientists across multiple fields related to mineralization, and providing networking and training to junior scientists in the field.

NIAMS, NIDCR, and other NIH components also co-funded a meeting in December 2010 on Pain and Musculoskeletal Disorders: Translating Scientific Advances into Practice. At the conference investigators from a range of disciplines discussed topics that included the role of neural factors in an individual's pain sensitivity, and how the latest research techniques in the pain field can be applied to joint disorder studies, including TMJD.

National Institute on Deafness and Other Communication Disorders (NIDCD)

Senate Significant Items

Item

Early Detection, Diagnosis and Intervention. - The Committee urges NIDCD to continue to study the speech, language, voice, auditory and psychosocial outcomes of children identified with hearing loss through newborn screening, including evaluation of different sound amplification strategies (including multiple hearing aid fittings) on perception and understanding; the impact of complex listening environments, such as noisy classrooms, on hearing aid performance; and the effects of parental engagement and delivery of services on emotional well-being. The Committee also recommends continuing study of the neurological basis of variability in outcomes in children with cochlear implants. (p. 100)

Action taken or to be taken

Approximately two to three in every 1,000 children in the United States are born with severe to profound deafness. In 1989, less than five percent of newborns received hearing screening prior to leaving the hospital and most children were not identified to have a hearing impairment until two to three years of age. That delay during a critical period for language development led to lifelong difficulties in language acquisition and the need for costly special education in schools for the deaf. The implementation of universal newborn hearing screening, a joint effort by NIDCD, the Health Resources and Services Administration, and the Centers for Disease Control and Prevention, has dramatically improved the identification of infants with hearing loss early in life and accelerated the initiation of services for these children. Today, more than 95 percent of children are screened for hearing loss shortly after birth. NIDCD continues to examine the outcomes of children identified through newborn hearing screening.

NIDCD-supported scientists are working to identify optimal sound amplification strategies for children identified through newborn screening programs. Current studies are examining the use of multiple hearing aid fittings to improve speech perception and understanding, and to determine how complex listening environments (e.g., noisy classrooms) may impact hearing aid performance. For example, NIDCD-supported research is examining the benefits of an extended frequency bandwidth hearing aid versus a frequency lowering hearing aid on the audibility of the high frequency components of speech. In addition, NIDCD-supported scientists are exploring the psychosocial outcomes of children with mild to severe hearing loss, including how parental engagement and support and services delivery affect the long-term emotional well-being of the child.

The number of hearing-impaired children identified by newborn screening programs and receiving a cochlear implant (CI) prior to two years old is increasing, and many of these children are participating in mainstream classrooms. However, NIDCD-supported research has demonstrated that hearing-impaired children are still at significant risk for language, reading, and academic difficulties even if they are identified early and receive state-of-the-art intervention. In addition, there is significant variability in the speech and language outcomes of children who receive CIs. NIDCD-supported scientists are examining the neurological bases of these variations to improve clinical management strategies. NIDCD-supported scientists are also

studying how CIs and language experiences impact cognitive and social functioning as cochlear-implanted children enter school. One study is comparing the development of higher order language skills in implanted and normal-hearing children, and will document speech production and recognition, higher order cognitive skills, behavioral and social adjustment, quality of parent-child interactions, parental well-being, and health-related quality of life. Results from this and other studies will inform the development of learning strategies in the preschool years to best prepare children for the language demands of early elementary mainstream classrooms.

Item

Hair Cell Regeneration. - The Committee continues to place a high priority on research involving inner ear hair cell regeneration and stem cells. It applauds NIDCD's development of a system for making what appear to be functional hair cells from stem cells and recommends further studies in this area. The Committee encourages continuing development of in vitro assays to identify molecules involved in the differentiation of adult and embryonic stem cells into specific cell types used in communication, as well as research on how to regenerate connections between nerve cells that project to the brain and replacement hair cells. Also advocated are the continuation of gene transfer studies that have shown transcription factors are able to induce some non-sensory cells within the cochlea to develop as neurons. (p. 100)

Action taken or to be taken

NIDCD shares the Committee's priority on research directed at regenerating inner ear hair cells and study of stem cells. The new 2012-2016 NIDCD Strategic Plan for Research includes goals to identify genes and factors that promote regeneration, enabling stem cells to proliferate and subsequently to differentiate, as well as studies to determine how regenerated sensory cells establish connections with the nervous system.

NIDCD maintains an active grants portfolio with a broad range of approaches for hair cell and neuronal regeneration. At present, these approaches are being tested in mammalian animal models of hearing loss. NIDCD-supported scientists are studying whether new hair cells transplanted into the auditory system are able to connect with the brain, and are manipulating the environment of the inner ear to help transplanted hair cells survive and function. Others are developing stem cell approaches to reverse damage to the spiral ligament, a structure that maintains the proper electrically-charged environment necessary for the inner ear to detect sound. Another research team is developing improved vectors for targeted gene delivery to inner ear supporting cells and hair cells, with the ultimate goal of stimulating regeneration via gene therapy. NIDCD intramural scientists demonstrated in mice that many non-sensory cells within the inner ear retain the ability to develop as either mechanosensory hair cells or functional neurons. In particular, forced expression of specific transcription factors can direct equivalent non-sensory cells towards either a neuronal or a mechanosensory cell fate. However, the ability of non-sensory cells to assume either fate diminishes significantly with development, suggesting that similar changes in cell fate are probably not possible in adult inner ears. Future research will seek to understand why non-sensory cells lose the ability to respond to transcription factors over time.

NIDCD funding also supports high throughput approaches to identify genes, regulators, and other important pathways in hair cell and support cell repair and regeneration. NIDCD oversees a Common Fund activity known as Protein Capture, designed to generate reagents to allow capture and study of proteins of interest in a particular biological process, including hair cell regeneration and maintenance.

In September 2011, NIDCD sponsored a workshop on biological and cell-based therapies for hearing and balance deficits. Scientific experts in attendance identified areas of outstanding current and future research promise. NIDCD is using this information to ensure that the Institute is allocating sufficient priority to the most promising research in regeneration, repair, cell-based gene therapy, and prevention.

Item

Hearing Aids and Cochlear Implants. - The Committee is pleased that NIDCD has launched a series of research initiatives between clinicians and researchers based on recommendations from a 2009 NIDCD Working Group on Accessible and Affordable Health Care for Adults with Mild to Moderate Hearing Loss. The Committee urges continuing collaborations between industry, scientists, clinicians and consumers in the area of low-cost hearing aids so that more of the population who need hearing aids can obtain them at affordable costs. The Committee is aware that some individuals need alternative hearing prostheses and therefore recommends additional studies evaluating the "bimodal" option of an implant in one ear and a hearing aid in the other as well as the option of implanting a short electrode, which combines electric and acoustical stimulation in the same ear. (p. 100-101)

Action taken or to be taken

Approximately 17 percent (36 million) of American adults report having some degree of hearing loss. Nearly half of adults ages 75 years and older have hearing loss. The hearing aid is the primary device available for managing hearing loss. Despite significant improvements in hearing aid technology over recent decades, only 20 percent of Americans who could benefit from hearing aids actually use them. Even among hearing aid users, most have lived with hearing loss for more than ten years before seeking a hearing instrument and their impairment has progressed to moderate-to-severe levels. This is due to many reasons, including the perceived and actual benefits, cost, value (benefit relative to price) of hearing aids, stigma, and accessibility to hearing health care. Acting on recommendations emerging from a 2009 NIDCD Working Group on Accessible and Affordable Hearing Health Care for Adults with Mild to Moderate Hearing Loss, NIDCD has launched a series of five research initiatives to facilitate collaborations between clinicians and researchers in academic and industry settings to address the pressing public health need of improving the accessibility, affordability, and outcomes of hearing health care. Several grants have recently been funded in response to these initiatives. NIDCD-supported scientists are examining the differences in real world benefits between higher-cost and lower-cost hearing aids, with the goal of providing increased access to effective, lower cost, hearing health care for underserved older adults. In addition, a new research project examines the comparative effectiveness of three screening protocols for identifying hearing loss in older adults within a primary care setting and on the subsequent use of hearing health services. Finally, NIDCD-supported scientists are developing and testing an automated hearing screening kiosk designed to

motivate those who fail a screening test to follow up with a full hearing assessment, focusing on how results may vary for participants from different geographical and demographic backgrounds.

The cochlear implant constitutes a great tool in the management of severe-to-profound hearing loss. It is the most widely utilized neural prosthetic device worldwide. NIDCD has a long history of supporting the development of the cochlear implant. Recently, NIDCD-supported scientists have investigated alternative strategies for optimizing the selection and fitting of cochlear implants to markedly hearing-impaired individuals having predominantly high frequency hearing loss in one ear and appreciable residual low frequency hearing in the other or "better" ear. Research in both adults and children is underway evaluating the "bimodal" fitting alternative, involving a cochlear prosthesis implanted in one ear and a hearing aid fitted to the other ear. A more recent fitting strategy, under active clinical study, is combining electrical via a cochlear implant and acoustical stimulation (EAS) of the same ear through implanting a short electrode. This allows preservation of residual hearing in the lower frequencies and the possibility of acoustical stimulation with concurrent electrical stimulation. EAS stimulation with a short electrode array offers a viable treatment option for individuals who do not receive benefit from hearing aids and may not qualify for a cochlear implant, due to residual low-frequency hearing. Current research efforts are aimed at ascertaining the benefits of the EAS compared to bimodal hearing treatment approaches to enable clinicians to make data-driven clinical decisions and to develop optimal treatment options.

Item

Hearing Impairment Among Children and Young Adults. - The Committee urges additional research on children and young adults with unilateral hearing loss [UHL] from all modes of injury. In particular, it recommends further studies on educational and behavioral problems among children with UHL and development of strategies to minimize this risk. The Committee also supports additional research to understand the susceptibility of adolescents and young adults to develop noise-induced hearing loss. The Committee commends NIDCD for its public education efforts about the dangers of hearing loss from noise exposure, especially the "It's a Noisy Planet. Protect Their Hearing" campaign, which was expanded to include Spanish language publications. (p. 101)

Action taken or to be taken

Up to one in twenty school-aged children in the United States have a unilateral hearing loss (UHL) – when there is impaired hearing in one ear and normal hearing in the other ear. Historically, hearing health care professionals and educators did not consider UHL a significant risk to the normal development of communication and academic skills in children. However, it is now known that children with UHL are at increased risk of educational and behavioral problems. NIDCD-supported research has shown that elementary school-aged children with UHL have poorer spoken language skills and lower vocabulary scores than their normal-hearing siblings. Furthermore, greater proportions of children with UHL receive speech/language therapy and require special educational assistance than their normal-hearing peers.

NIDCD-supported scientists are currently using functional imaging technology to study the brain organization and auditory processing abilities of children with UHL. Early results suggest that

UHL affects the organization of the brain and limits the ways auditory processing tasks are accomplished. Understanding these differences between normal hearing and UHL children may help inform the development of interventions to minimize the risk of children with UHL experiencing diminished educational outcomes.

NIDCD is also working to understand better the susceptibility of young adults developing noise-induced hearing loss (NIHL). For example, an NIDCD-supported project is measuring the hearing thresholds and noise exposure levels of one thousand participants between 18-25 years of age. The researchers are comparing the prevalence of several genetic variations associated with NIHL in these individuals to determine whether there are gene-environment interactions, particularly when correlated with reported lifetime noise exposure.

Early education about the dangers of loud noise exposure and how to prevent damage to the inner ear is an important step in minimizing NIHL in future generations. Towards this end, NIDCD continues to promote early education of elementary and middle-school children about NIHL and how to prevent it through NIDCD's *It's a Noisy Planet. Protect their Hearing Campaign*. This campaign brings the message of hearing health and hearing protection into classrooms and living rooms through fun, interactive presentations, websites, and brochures.

Item

Hearing Loss. - The Committee is aware that loud and prolonged noise can permanently damage hearing. The Committee continues to encourage the Department to educate the public about the importance of protecting their hearing, through public service announcements or other means, as there is no cure for deafness caused by exposure to loud noise. (p. 154)

Action taken or to be taken

Early education about the dangers of loud noise exposure and how to prevent damage to the inner ear is an important step in minimizing noise-induced hearing loss (NIHL) in future generations. Towards this end, NIDCD launched *It's a Noisy Planet. Protect Their Hearing* campaign in 2008. The Noisy Planet campaign is designed to increase awareness among parents of children ages 8 to 12 (an age group known as “tweens”) about the causes and prevention of NIHL. With this information, parents and other caring adults can encourage children to adopt healthy habits that will help them protect their hearing for life.

The Noisy Planet website features downloadable fact sheets, posters, bookmarks, and other educational materials that have been developed to address specialized topics pertaining to NIHL for parents and tweens. Among these are materials in English and Spanish as well as those targeting rural families and low-literacy audiences. In addition, the website is continuously updated with new information to engage new and existing audiences. NIDCD is also exploring new ways to engage and broaden audiences through the Noisy Planet Facebook page and other social media.

In 2011, the Noisy Planet campaign released four public service announcements (PSAs), two in English and two in Spanish, for print and radio coinciding with the release of materials for Spanish-speaking and rural audiences. The PSAs emphasized the availability of new Spanish-

language materials and the importance of protecting children's hearing on the farm. As of January 2012, the rural radio announcement in English has been broadcast more than 450 times in 37 states, the Spanish version has been broadcast more than 80 times in eight states, and newspaper articles have been published in more than 100 (English) and 150 (Spanish-language) newspapers.

NIDCD has helped extend the outreach of the Noisy Planet campaign by staffing the Noisy Planet exhibits at health fairs and conferences, including the National Association of School Nurses, National Science Teachers Association, National Association of Elementary School Principals, and Future Farmers of America. In addition, NIDCD has developed partnerships with the American Speech-Language-Hearing Association, Hearing Health Foundation (formerly Deafness Research Foundation), 4-H, Acoustical Society of America, and other organizations, to help disseminate Noisy Planet information to their members and constituency groups. In addition, for the past two years, NIDCD has been traveling to local elementary and middle schools to deliver a 45-minute presentation about the science of sound and how to protect our hearing from excessive noise, reaching more than 3,000 students to date.

Item

Hereditary Hearing Loss. - The Committee encourages additional efforts by NIDCD to identify and understand the structure, function and regulation of genes whose mutation results in deafness and other communication disorders. (p. 101)

Action taken or to be taken

NIDCD-supported scientists are actively working to understand how the structure, function, and regulation of genes results in deafness and other communication disorders. For example, using state-of-the-art targeted genomic capture and massively parallel sequencing technologies, one NIDCD-supported scientist and her team have identified genes for hereditary hearing loss in six hearing impaired individuals and their families. The original six genes led to the identification of causative gene mutations in 20 additional deaf individuals and their families. Another team of NIDCD intramural scientists identified a novel gene for nonsyndromic deafness, which is inherited hearing loss or deafness without other symptoms). Mutations of the novel deafness gene, called TPRN, which encodes the protein taperin, were revealed to be responsible for some cases of nonsyndromic deafness. In inner ear hair cells, taperin is localized to a region at the base of stereocilia, the tiny hair-like projections jutting from the top of cells in bundles that help transform sound energy into electrical energy. In addition, a second team of NIDCD intramural scientists identified a gene called GIPC3 as the basis for one form of adult-onset hearing loss, and determined how mutations in GIPC3 gene result in unstable proteins. These and other teams of NIDCD-supported scientists are now working to characterize the proteins encoded by the identified deafness genes, and further our understanding of the biological mechanisms involved in hearing loss.

NIDCD is supporting development of an integrated relational database of genetic, audiologic, otologic, and other medical data. The database will enable researchers and clinicians to study more effectively how underlying genetic and environmental factors influence the effectiveness and outcome of patient-directed therapies and interventions. This work will help healthcare

professionals identify pediatric patients at high risk for congenital or late onset hearing loss, assess the audiologic and otologic features of children with all forms of hearing loss, and characterize the genetic basis for hearing loss.

NIDCD is also supporting research projects that will utilize basic research findings and translate them into clinical tools. For example, one NIDCD-supported scientist is working to make comprehensive genetic testing for deafness available to clinicians for under \$500 per person. This will result in the establishment of genetic screening as an important diagnostic test for deafness, following medical history and physical exam.

Item

Noise-Induced Hearing Loss. - The Committee continues to put a high priority on better understanding and preventing noise-induced hearing loss. In particular, the Committee encourages NIDCD to support environmental and genetics studies assessing predisposition to noise-induced hearing loss and additional research on the use of antioxidants and other micronutrients to prevent cell death in the inner ear. Genetic and proteomic studies in zebrafish concerning the effect of ototoxic drugs on hair cells are also encouraged. (p. 101)

Action taken or to be taken

Protecting individuals from, and treating individuals with, noise induced hearing loss (NIHL) is a high priority for NIDCD. Prevention of noise-induced hearing loss would improve quality of life for the millions exposed to noise, and decrease healthcare costs for individuals, businesses, and government agencies.

It is known that acoustic overexposure can cause noise-induced hearing loss and that there is considerable variability in susceptibility to NIHL between individuals. To understand this variability and identify factors which may predispose people to develop NIHL, NIDCD-supported scientists are measuring hearing thresholds and noise exposure levels of one thousand young adults between 18-25 years of age. The scientists will also examine participants for several genetic variations associated with NIHL to determine whether there are significant gene-environment interactions that contribute to the development of NIHL.

NIDCD-supported scientists are also examining the use of antioxidants and other micronutrients to protect against NIHL. For example, one group's research in animal models is exploring the usefulness of antioxidant therapy to protect the connections between inner hair cells and the auditory nerve from damage due to excessive noise. Another group is examining the use of a combination of FDA-approved drugs for the treatment and prevention of NIHL. Finally, in an NIDCD-supported phase II clinical trial, scientists are investigating the efficacy of chronic administration of antioxidants and a vasodilator in reducing or preventing NIHL following exposure to loud music or military training exercises.

Identification of drugs that may reduce or eliminate ototoxicity from commonly used antibiotics or chemotherapeutics is of high priority to NIDCD. Using high throughput screening and a zebrafish model system, NIDCD-supported scientists have identified compounds that can protect against ototoxicity. These compounds are now being further developed through the

Neurotherapeutics Grand Challenge program of the NIH Blueprint for Neuroscience. In addition, NIDCD intramural scientists are currently working in an *in vitro* mouse model to develop a treatment paradigm to prevent hearing loss induced by cisplatin, an ototoxic drug commonly used for chemotherapy.

Item

Otitis Media. - The Committee recognizes the threat to infants' and children's health and development from ear infection, or otitis media. The Committee therefore urges NIDCD to accelerate its research on the pathogenesis of ear infection and its consequences. In particular, it urges additional studies of genetic risk factors, new treatments for chronic and recurrent otitis media, and new methods for the delivery of drugs to the middle ear. (p. 101)

Action taken or to be taken

Otitis Media (OM), or middle ear infection, is one of the most common reasons for a sick infant to visit a doctor. Seventy-five percent of children experience at least one episode of OM by their third birthday, and almost half of these children will have three or more ear infections during their first three years. The medical costs and lost wages resulting from OM amount to billions of dollars in the U.S. each year. OM often begins when viral or bacterial infections that cause sore throats, colds, or other respiratory or breathing problems spread to the middle ear. NIDCD supports research on how the bacterium, *Streptococcus pneumoniae* (Spn) - a leading cause of OM - colonizes the normal middle ear. New methods will be developed to identify Spn virulence genes uniquely expressed in settings with multiple different microbes. This study will aid in the development of therapeutics, provide information relevant for the control of other bacterial pathogens that colonize the respiratory tract, and also facilitate development of prevention strategies for other common bacterial pathogens.

NIDCD also supports a wide variety of studies to develop new treatments for chronic and recurrent OM. These studies examine the bacterial pathogenesis and human immune responses following infection, how genetic risk factors make individuals more or less susceptible to OM, especially in children born with a genetic predisposition and those exposed to OM environmental risks, and whether environmental factors could modify OM risks in children with a genetic predisposition. In addition, NIDCD supports research to develop new methods for delivery of drugs to the middle ear. For instance, NIDCD is funding a study on trans-tympanic (i.e., across the ear drum) treatment of OM. The purpose of this study is to develop a means of treating middle ear infections by applying an antibiotic gel once in the outer ear. The chemicals in the gel will help antibiotics cross the eardrum and the gel holds the medicine in place. This approach may help prevent antibiotic resistance and toxicity by keeping the medications localized. NIDCD is also funding studies with the ultimate intent of developing vaccines against OM. NIDCD-supported scientists are evaluating how well two novel, live, attenuated Spn vaccines work against OM in a mouse model and may be developed into an effective intranasal vaccine.

Item

Plasticity. - The Committee continues to support research on functional changes of neurons and synapses of the central auditory nervous system during development and following hearing loss.

Specifically, the Committee encourages the continuation of brain-imaging research in children with severe to profound unilateral hearing loss to understand the reorganization that occurs to process sound, speech and language, as well as experiments in animals to understand perceptual and neural coding changes in the auditory cortex during conductive hearing loss and after restoration of normal hearing. (p. 101-102)

Action taken or to be taken

Neuroplasticity is the ability of the nervous system to change and adapt in response to the environment. NIDCD supports research on how neuronal and synaptic plasticity in auditory central nervous system pathways is relevant to developmental hearing loss. Using a mouse model for neurophysiology and pharmacology studies, NIDCD-supported scientists are assessing the plasticity of the brain regions involved in hearing. They will study the impact of noise-induced hearing loss on nerve synapse connectivity and synapse plasticity. Identification of key circuits and cellular mechanisms supporting this plasticity is critical to understanding how the brain adapts to hearing loss.

Other NIDCD-supported scientists are using brain imaging technology to study children who have severe-to-profound hearing loss in one ear and observing how the child's brain activates in response to sound, speech, and language. A recently completed study on these children showed that the areas of their brain associated with hearing were less active in understanding speech in a noisy environment in comparison to children without hearing loss. These findings require further investigation to determine whether inadequate brain reorganization will result in loss of particular mechanisms involved in process speech in noise. If so, there is greater need for these children to require remediation techniques such as hearing aids.

In addition, NIDCD-supported scientists are using animals as models for children who develop ear infections (otitis media, OM) that result in fluid build-up (effusion) that blocks sounds traveling into the inner ear. Studies with these animal models are designed to determine how the auditory cortex is changed by the loss of hearing during early development. The impact of conductive hearing loss (CHL) may persist for years, but little is known about how the brain is affected. Using a rodent model, scientists can experimentally induce and reverse CHL to resemble the effects of childhood OM with effusion. This model enables scientists to observe the plastic changes at the level of individual neurons and their synapses. The current efforts are identifying mechanisms activated during the onset of a hearing loss and when hearing is later restored. Another study uses a rodent model to test whether auditory training can improve the ability to process speech after CHL. Scientists discovered that using training techniques with young animals can improve the ability of adults to detect sound against a noisy background. This rescue of perceptual skills by training the young is an important consideration for therapeutic interventions following CHL in children and demonstrates plasticity in the developing auditory system.

Item

Presbycusis. - The Committee urges NIDCD to continue multidisciplinary physiological and neurological studies of the peripheral and central mechanisms of presbycusis, or age-related hearing loss. It commends NIDCD's support of a P50 Specialized Center on Experimental and

Clinical Studies of Presbycusis. The Committee also recommends support for temporal bone banks so that inner ear bones from individuals diagnosed with presbycusis can be studied. (p. 102)

Action taken or to be taken

Presbycusis is gradual hearing loss that occurs in most individuals as they grow older. Approximately 40 percent of adults between the ages of 65 and 74 years, and nearly 75 percent for people aged 75 and older, have a hearing loss. NIDCD considers presbycusis an area of great importance and supports research on how age-related hearing loss is caused by the complex interaction of inherited genes and environmental exposures.

NIDCD continues to support a Specialized Center on Experimental and Clinical Studies of Presbycusis. This multidisciplinary Center focuses on improving diagnostic, rehabilitative, and preventive measures for age-related hearing loss. Research at the center is currently addressing basic questions related to the understanding of speech and the benefit of hearing aids in realistic listening environments by older adults. One reason frequently cited for low hearing aid use is the aids' inability to help the user distinguish speech from noise. Therefore, scientists supported by the Center are currently working to determine how to change amplification settings to provide an increase in hearing-aid benefit in real-life situations. Recent studies in an animal model suggest that caloric restriction (eating less) may be able to delay the onset of age-related hearing loss. NIDCD is supporting a study examining the molecular basis for this effect, to determine whether protecting the inner ear from oxidative stress – a chemical breakdown process that produces damaging free-radicals - may slow age-related hearing loss. Such studies have the potential to provide the foundations for future preventative therapies. Other NIDCD-funded studies are examining the age-related changes in spiral ganglion nerve cells, which relay auditory information from the sensory hair cells of the inner ear to the brain. These nerve cells are critical for proper auditory function, and understanding how their properties change during aging may provide insights into avenues for future interventions.

To understand changes in shape and function that occur due to age-related hearing loss or other human inner ear diseases, scientists study human temporal bones, which house the inner ear. These temporal bones are donated for research and harvested after death. NIDCD supports temporal bone laboratories that act as both banks and research laboratories to retain and study specimens of human inner ear tissue, for research on presbycusis and other structurally-related hearing conditions. To combine the expertise of these temporal bone laboratories, NIDCD established the NIDCD Otopathology Research Collaboration Network to support collaborative studies of temporal bone research on human ear disorders, including presbycusis. The laboratories that comprise this Network apply modern imaging, biochemical, and molecular biological tools to the study of human presbycusis and other inner ear disorders. To facilitate temporal bone donations, NIDCD funds the NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry to disseminate information about temporal bone donation and to enroll donors.

Item

Synapse Function. - The use of hearing aids and cochlear implants may be limited by dramatic changes in synapse connections following developmental hearing loss. Recognizing this, the Committee supports research on genetic and cellular mechanisms of normal synapse function and on approaches to prevent or reverse deafness caused disruptions that affect one's ability to benefit from aids or implants. (p. 101)

Action taken or to be taken

Nerves communicate with each other at specialized junction sites called synapses. These sites enable an impulse to be transmitted, by electrical or chemical means, from one nerve to another. Synapses exhibit great diversity and specialization for transmitting different types of information. They are shaped by genetic and cellular processes as well as by development, experience, and learning. Hearing loss results in widespread changes in the neural circuitry of the auditory system as well as changes in the properties of synaptic transmission. These changes have important implications for restoring hearing function via cochlear implants or hearing aids.

NIDCD-supported scientists are studying mechanisms of normal synaptic transmission that is necessary for sound processing by the cochlea. Examples of research focusing on the normal synaptic transmission of the sensory hair cells of the inner ear include the regulation of synaptic vesicle release, identifying the interactions of inner ear synaptic proteins, and understanding how ion channels regulate synaptic vesicle release and firing rate of nerve impulses. In addition, NIDCD intramural scientists have developed techniques to record sound-evoked responses from the neurons in a mouse. This enables scientists to understand the function of synapses in different types of neurons.

NIDCD also supports research on disordered synaptic transmission which can cause hearing impairment. Scientists used animal models to show that noise exposure previously believed to be at a non-damaging level does indeed compromise the integrity of auditory synapses. It is important to understand the effects of noise on synapse function and the long term consequences on sensorineural hearing loss. In another NIDCD-supported project, scientists are exploring the usefulness of antioxidant therapy and other treatments to protect the synaptic connections between inner hair cells and the auditory nerve from damage due to insertion of auditory prostheses.

Hearing loss at an early age can have dramatic effects on synaptic function. Scientists recently discovered that during maturation of a congenitally deaf animal model, abnormalities appear in synapses which connect the auditory nerve to the brainstem. Previous studies with this animal model have shown that these synapses can be rescued by electrical stimulation provided by a cochlear implant, so understanding the progression of abnormal synapse development may help inform physicians on the benefit of providing children with either one or two cochlear implants.

Item

Tinnitus. - The Committee urges NIDCD to address the lack of knowledge about the specific neural dysfunction responsible for tinnitus. It also encourages research on the prevention, treatment and cure of this prevalent disorder, including identifying chemicals to prevent

development of chronic tinnitus; developing preventative delivery methods for ototoxic drugs; and discovering treatments to suppress hearing-system hyperactivity. (p. 102)

Action taken or to be taken

Tinnitus is a major health concern and its severity can range from a mild condition, which requires no intervention to a severe debilitating disease with significant emotional, social, and economic impact. The estimated number of Americans who have experienced this “ringing in the ears” is currently 25 million, but this number is expected to grow over time, primarily due to an increased average age of the population. Tinnitus is also the most prevalent service-connected disability of American veterans, with more than 744,000 veterans receiving disability compensation for tinnitus as of the end of FY 2010.

NIDCD continues to support research that advances our understanding of specific changes in neural function that give rise to tinnitus. Recently, NIDCD-supported scientists reported that stimulation of the vagus nerve (a large nerve that runs from the head to the abdomen) with an implantable electrode, in combination with the playing of tones, is able to eliminate evidence of tinnitus in rats. (Vagus nerve stimulation is already in use for the treatment of epilepsy and depression in more than 50,000 individuals). These exciting findings are the first demonstration of a treatment that specifically erases the tinnitus percept, rather than simply masking the sound or providing coping mechanisms for the individual. Scientists are now working to translate these findings from the animal model into a novel therapeutic strategy for people with severe tinnitus. Other NIDCD-supported scientists recently identified parts of the brain not involved in hearing that contribute to the development of tinnitus. This project provides strong evidence of the changes in brain connections that lead to tinnitus, and may also explain why almost all people with tinnitus have some hearing loss, but not everyone with hearing loss goes on to experience tinnitus.

NIDCD Intramural scientists are continuing brain imaging studies to determine the neural basis of tinnitus. Recent studies have identified structural changes in the brain associated with hearing loss or tinnitus, as well as the involvement of other brain regions for attention or short-term memory in the development of chronic tinnitus.

Clinical trials are also underway to prevent and treat tinnitus. An NIDCD-supported phase III clinical trial is determining the efficacy of Tinnitus Retraining Therapy in people with chronic, debilitating tinnitus. Tinnitus Retraining Therapy combines counseling, to neutralize negative emotional reactions to the tinnitus, and sound therapy, to reduce awareness of the tinnitus, to restore quality of life. In addition, NIDCD is supporting a phase II clinical trial studying the use of repetitive transcranial magnetic stimulation (rTMS) in tinnitus patients. Brain imaging studies have shown that tinnitus is associated with hyperactivity of a variety of brain regions. rTMS applies frequent, repeated magnetic stimuli outside the skull to induce changes in brain activity. rTMS is believed to lessen tinnitus by inhibiting hyperactivity related to tinnitus. The trial is assessing clinical improvement and structural brain remodeling associated with rTMS treatment, and identifying factors that could predict outcomes of rTMS treatment. Finally, in an NIDCD-supported phase II clinical trial, scientists are investigating the efficacy of chronic administration of antioxidants and a vasodilator in reducing or preventing noise-induced hearing loss and tinnitus following exposure to loud music or military training exercises.

Item

Translational Research. - The Committee recommends additional research activities and clinical trials on the prevention and treatment of hearing loss from noise, drugs, aging, and genetic causes, and translation of these studies to therapies. Clinical trials relevant to Meniere's disease, sudden deafness and autoimmune inner ear disease are encouraged. (p. 102)

Action taken or to be taken

NIDCD actively encourages the translation of basic science discoveries into intervention and therapies. For example, NIDCD sponsored a workshop in 2004 on Translational Research in Hearing and Balance to facilitate the translation of basic biomedical or behavioral research discoveries into new clinical and research tools, prostheses and assistive devices, behavioral, pharmacotherapeutic, and surgical therapies. The resulting Funding Opportunity Announcement remains active today and is promoting milestone-driven research. This initiative encourages industry collaboration when appropriate, and requires both clinical and basic scientists to be a part of the research team. The initiative continues to be a core mechanism for increasing translational research supported by NIDCD. Examples of projects include research on reversing age-related laryngeal muscle dysfunction, which can lead to voice disorders, the use of small molecules to rescue auditory nerves from degeneration, developing a brain-computer interface to help individuals with severe speech and physical impairments communicate, and developing an imaging instrument to measure the inner ear's blood flow for diagnosing and treating individuals with sudden sensorineural hearing loss and Meniere's disease.

In addition, NIDCD intramural scientists are conducting translational research aimed at preventing drug-induced hearing loss. Studies are underway on the effectiveness of a variety of protective molecules in preventing hearing loss from ototoxic drugs, and to develop methods that would either eliciting these molecules to be expressed or physically delivering the molecules to the inner ear. Intramural scientists are also testing FDA-approved drugs to determine if these compounds have protective effects against drug-induced hair cell death and hearing loss.

Although NIDCD is not currently supporting clinical trials specific to Meniere's disease, there are ongoing clinical trials on the prevention and treatment of noise-induced hearing loss, sudden deafness, and autoimmune inner ear disease. For example, a phase II clinical trial is currently investigating the efficacy of chronic administration of antioxidants (vitamins A, C, E, and magnesium) and a vasodilator in reducing or preventing noise-induced hearing loss. Two real-world noise insults are studied - loud music under laboratory conditions and military urban warfare training exercises. Scientists conducting a phase III clinical trial have concluded that steroids injected behind the eardrum (which then enter the inner ear) have comparable benefit to using steroid pills in treating individuals with sudden deafness. Some individuals cannot take steroid pills orally because of high blood pressure, diabetes, or other conditions. This trial shows they can be alternatively treated with steroid injections across the eardrum without aggravating these problems. In a phase I clinical trial, scientists are investigating the efficacy and safety of a new treatment for autoimmune hearing loss when the loss fails to respond to traditional oral steroid treatment. Scientists have obtained preliminary evidence that anakinra, a drug that blocks a central immune pathway, restores hearing in some steroid-resistant patients with autoimmune hearing loss.

Item

Usher Syndrome. - The Committee encourages NIDCD to continue to support genetic research into Usher syndrome, the most common condition that affects both hearing and vision. (p. 102)

Action taken or to be taken

Usher syndrome (USH) is a genetic disorder, which affects both hearing and vision. Usher syndrome is recessively inherited and characterized by hearing loss, retinitis pigmentosa (RP) and, in some cases, a balance (vestibular) disorder. Approximately three to six percent of all deaf children and perhaps another three to six percent of hard-of-hearing children have Usher syndrome. In developed countries such as the United States, about four babies in every 100,000 births have USH. The syndrome is both genetically and phenotypically diverse, with three identified clinical manifestations (Type I, II, and III) and at least 12 identified genetic regions involved, including genes encoding the proteins cadherin 23 and protocadherin 15. The severity of the hearing loss and the presence of vestibular dysfunction distinguish two major clinical subtypes of USH, types I and II. Individuals who have USH type I are deaf and have a balance deficiency at birth, with onset of RP occurring in these individuals at about the time of puberty. Individuals with USH type II are distinguished from USH type I in having a less severe hearing loss. USH type III is characterized by progressive loss of hearing and retinal function.

NIDCD-supported scientists are currently examining how proteins encoded by two deafness genes, cadherin 23 and protocadherin 15, assemble to form the mechanosensory apparatus of hair cells. This work will substantially add to our understanding of hair cell function and help develop strategies to treat inherited deafness. In addition, NIDCD-supported scientists are studying *clarin1*, the gene involved in USH type IIIA, in an animal model. This work may shed light on the cause of this devastating disorder and provide means for prevention or treatment. Other NIDCD-supported scientists are analyzing how mutations in Myosin VIIA, a cellular motor protein expressed in several tissues, including the inner ear and the retina, play a role in USH type IB. USH type IB is known to be caused by two recessive mutations in the genes *DFNA11* and *DFNB2*.

NIDCD intramural scientists have identified and characterized some of the genes responsible for USH and common recessive mutations that cause USH (Types I and II) in the Ashkenazi Jewish population. In addition, several NIDCD-supported scientists reported cloning the gene responsible for USH type IIA. The *USH2A* gene encodes a protein, Usherin, that has structures similar to other proteins involved in assembling cells and tissues into functional organs. NIDCD intramural scientists are also working in collaboration with the National Eye Institute on a natural history study of USH to identify the genetic phenotypes of the auditory and vestibular function of people with this syndrome. The identification of genetic mutations which cause the disease will enable the development of effective screening methods so affected individuals can begin interventions as early as possible, prior to loss of vision and hearing. In addition, understanding the molecular changes in the genes and proteins they encode will increase understanding of the etiology and progression of the disease, potentially informing future treatments.

Item

Vestibular Research. - The Committee continues to urge the NIDCD to conduct vestibular research in animal models and humans. (p. 102)

Action taken or to be taken

The vestibular system of the inner ear provides the brain with sensory information needed for balance, eye stabilization, posture, and locomotion. Vestibular disorders cause dizziness and problems with balance, and affect an estimated 10 million adults in America. NIDCD's support of vestibular research includes basic research on the neural mechanisms of vestibular sensory function in animals and humans, and clinical research on human perceptions and disorders.

Turning the head stimulates the semicircular canal system in the inner ear. In response to this motion, an eye reflex called the vestibulo-ocular response (VOR) stabilizes the gaze. Measuring the VOR is a well-known method to evaluate vestibular function. NIDCD-funded scientists are studying how nerve cell signals from the vestibular system interact with a part of the brain called the cerebellum to help an animal adapt its VOR response when inputs are changed, such as in the loss of vestibular sensations on one side of the head.

Vestibular information about balance and head position is used in many ways throughout the body. Positional information helps mediate rapid changes in local blood pressure to maintain blood flow to the brain when rising to stand up after lying down, and to prevent blood pooling in lower extremities when standing. Failure of this system is called orthostatic intolerance, and can lead to fainting and longer-term disabilities. Medications used to treat high blood pressure often have the unwanted side-effect of causing dizziness and vertigo, especially in elderly individuals. NIDCD-supported scientists previously determined that blood pressure medications act on a part of the brain that not only regulates blood pressure, but also receives input about balance. NIDCD-funded scientists have begun to map circuits in this part of the rat brain using a new molecular tracing technique. These studies are helping to clarify how connections with sympathetic nervous system neurons mediate the blood pressure response. The results may help scientists design new blood pressure medications that do not interfere with the local, rapid changes in blood pressure (orthostatic regulation) necessary for everyday life.

Vestibular perception has been difficult to define, and we know little about the brain circuits involved in converting vestibular stimulation to sensation (the feeling of where one is in space) and perception of self-movement. NIDCD-supported scientists are studying the brains of non-human primates trained in perceptual tasks to understand how vestibular inputs from the inner ear are combined to produce spatial perception. This research is relevant to disorders affecting posture and the human sensory disorder of vertigo.

Scientists are working to develop a vestibular prosthesis to replace balance and positional information lost through disorders like Ménière's disease or head trauma. NIDCD currently supports several projects using animal models to work toward this translational goal. Implantable devices have been developed and are being tested in non-human primates. All groups have reported results indicating that the vestibular nerve can be safely, effectively, and specifically stimulated electrically to drive responses that mimic normal vestibular responses.

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National Institute of Mental Health (NIMH)

Senate Significant Items

Item

HIV/AIDS Behavioral Research. - The Committee supports NIMH's critical work in developing behavioral interventions to prevent the spread of HIV/AIDS across multiple populations as well as addressing co-morbid mental and substance abuse disorders. The Committee recognizes that new research is needed to ensure the long-term maintenance of behavior changes as HIV/AIDS has become a chronic disease. Behavioral research aimed at reducing the likelihood of HIV infection should include structural, environmental and socioeconomic variables to ensure that research-based interventions can be evaluated as appropriate for racial and ethnic minority populations. (p. 104)

Action taken or to be taken

The National Institute of Mental Health (NIMH) is committed to supporting research to decrease the incidence and morbidity of HIV/AIDS, with an increasing focus on racial and ethnic minority populations who have the highest rates of new infections. NIMH research efforts are building on a chronic disease framework, which emphasizes the need for treatment and prevention effects to be maintained for the long term and explores common issues that may underlie multiple chronic conditions, such as behavioral self-management. Recent advances in the HIV/AIDS prevention raise the realistic possibility of transformative reduction in HIV/AIDS transmission. This is particularly critical in racial and ethnic minority populations who face multiple social and economic barriers to pursuing and maintaining treatment. The barrier to realizing this goal predominantly is the lack of effective behavioral tools; strategies are needed to engage people in HIV testing, link them to care, and promote adherence to long term prevention and care. Current NIMH efforts are directed towards expanding the integration of behavioral science with biomedical approaches, which is critical to developing and implementing the combination intervention approaches that are necessary to significantly impact the epidemic. Furthermore, NIMH is working to integrate behavioral and biomedical approaches through the expansion of collaborations across NIH and other federal agencies in order to leverage resources and broaden the impact of this research.

To advance research on HIV/AIDS, NIMH has recently published two funding opportunity announcements (FOA). The first FOA ("Discovery, Development, and Testing of Novel Interventions to Advance HIV Prevention and Care;" PA-11-275) encourages novel, high impact research that will contribute to the creation of empirically-based HIV/AIDS-risk reduction approaches that could be used to pave the way for prevention, reduction of clinical symptoms, and cure. Specific goals of the FOA include research to advance combination behavioral-biomedical approaches to HIV/AIDS-related interventions; develop strategies to improve long term maintenance of interventions and promote treatment adherence; enhance prevention efforts targeting high risk, vulnerable populations, including development of interventions to reduce racial/ethnic, gender, and age-related disparities in HIV treatment and treatment outcomes; identify new behavioral targets and intervention approaches within multiple intervention areas; and incorporate context (e.g., cultural and social factors) into intervention development and testing, thereby advancing the development and testing of

interventions delivered beyond the individual level. The second FOA (“Advancing the Impact of Effective HIV/AIDS Prevention and Treatment Interventions;” PA-11-271) is designed to increase the impact of effective HIV/AIDS-related interventions for prevention and treatment. Specifically, research is solicited to develop the capacity to close the gap between the development of new, research-tested interventions and their widespread use by those most in need. The two overarching goals of this FOA are to encourage projects that will improve the uptake of efficacious interventions and conduct research to inform and enhance the effectiveness and efficiency of interventions in order to maximize community impact.

Item

Premature Mortality. - The Committee continues to be concerned about premature mortality and lower life expectancy experienced by adults living with serious mental illness as result of treatable medical conditions such as cardiovascular, pulmonary, endocrine, and infectious diseases. The Committee urges NIMH to collaborate with other institutes including NIDDK and NHLBI on a focused research program into the causes and interventions needed to address this crisis. The Committee requests an update on this topic in the fiscal year 2013 budget justification. (p. 104)

Action taken or to be taken

Research has shown a striking disparity in life expectancy for individuals with serious mental illness (SMI) in the United States. On average, Americans with SMI die between 14 to 32 years earlier than the general population. To address this pressing issue, the National Institute of Mental Health (NIMH) supports numerous studies, including co-sponsored research with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute on Drug Abuse (NIDA), which aim to improve the general health of adults with SMI. These studies focus on a broad range of treatable conditions found to be associated with SMI that harm the health of these individuals (e.g., nicotine addiction, diabetes, and cardiovascular disease) and contribute to their premature mortality. NIH is also focusing on the metabolic syndrome that may result as a serious side effect of medications that individuals with SMI take to treat their mental illness. This syndrome often results in obesity and high blood pressure, increasing the risk for heart disease and other health conditions.

NIMH and NIDDK recently co-funded a landmark study to improve care for patients with both depression and diabetes. The researchers examined a primary care approach called *TEAMCare* in which nurses worked with patients and their physicians to manage care for depression and poorly controlled diabetes in an integrated fashion, using evidence-based care guidelines. The study found that *TEAMCare* patients experienced less depression, better control of blood sugar, improved quality of life, and higher satisfaction with care, as compared to patients receiving usual care. To address the metabolic syndrome resulting from medications used by people with SMI, NIMH and NIDDK jointly issued a program announcement (PA) titled “Adverse Metabolic Side Effects of Second Generation Psychotropic Medications Leading to Obesity and Increased Diabetes Risk” (PAR-08-160). Several innovative studies have been funded under this PA. NHLBI maintains a vigorous research program on the associations between depression and cardiovascular disease, including studies to understand the underlying behavioral, physiological,

and genetic mechanisms, as well as efforts to develop effective clinical interventions and preventive strategies. For example, NHLBI and NIMH are collaborating to establish and conduct research through the new HMO Research Network Cardiovascular Research Network.

Also, in 2010, NIMH, NHLBI, and NIDDK, together with other NIH Institutes, convened a workgroup focused on improving care for patients with co-occurring medical conditions, especially depression and diabetes, in primary care settings. The workgroup is now in the process of developing a funding opportunity announcement to further encourage research on practical approaches for integrating and improving care for these patients with co-occurring disorders. The findings from these research collaborations will improve our understanding of how these disorders are related, how we can improve intervention and treatment, and represent the first steps toward reducing premature mortality for persons living with serious comorbid mental and physical illnesses.

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National Institute on Drug Abuse (NIDA)

Senate Significant Items

Item

Blending Initiative. - The Committee is concerned that NIDA has reduced funding for activities that help State substance abuse agencies infuse into the Nation's publicly funded substance abuse system the knowledge gained by NIDA's research. In particular, the Committee is concerned that NIDA reduced funds for its Blending Initiative, which supported a dialogue between NIDA, SAMHSA and State substance abuse agencies on "research to practice" and "practice to research" activities. The Committee urges NIDA to allocate funding to re-engage State substance abuse agencies on this important issue. (p. 103)

Action taken or to be taken

Accelerating the dissemination of research-based drug abuse treatment findings into front-line clinical practice is critical to improving drug abuse treatment and represents the core mission of the Blending Initiative. NIDA's Center for Clinical Trials Network oversees the Blending contract, funded at the same level as in previous years and complemented by an ongoing interagency agreement with the Substance Abuse and Mental Health Services Administration (SAMHSA) to co-fund multiple Addiction Technology Transfer Centers (<http://www.attcnetwork.org/index.asp>).

The collaboration between NIDA's National Drug Abuse Treatment Clinical Trials Network and SAMHSA's Addiction Technology Transfer Centers to develop research-based "products" and to train treatment providers in their use remains at the core of the Blending Initiative. This approach helps ensure that treatments showing positive results are practical, that they align with community and provider needs and values, and that they are accepted and used by practitioners. NIDA also engages State substance abuse agencies and other institutions on moving "research to practice." Planned outreach to these entities will help identify strategies for accelerating the adoption of evidence-based practices into medical settings and drug abuse prevention and treatment programs.

To date, the Blending Initiative has produced seven products geared to different audiences: (1) buprenorphine treatment for use by multidisciplinary addiction professionals; (2) buprenorphine for treating opioid withdrawal; (3) buprenorphine treatment in young adults; (4) how to use the Addiction Severity Index in treatment planning; (5) how to implement motivational interviewing so that it is done correctly; (6) awareness and effective use of motivational incentives; and (7) a package of tools for clinicians and researchers using motivational incentives, which contains three user-friendly products to support implementation (i.e., training tools, an online course, and software). Two more Blending Initiative products are nearing final stages of development: one on buprenorphine as a treatment for prescription opioid addiction and another on increasing testing for HIV infection among drug users to reduce the spread of AIDS.

New efforts within the Blending Initiative include: (1) facilitating the use of electronic health records as a tool to link general health care clinicians with specialty substance abuse treatment providers; (2) expanding and improving the tools associated with different Blending Products

(e.g., a self-guided, interactive online course on adopting motivational incentives); (3) enhancing NIDA's Blending website to improve its usability and impact; and (4) supporting an upcoming conference (April 2012), to be held in conjunction with the annual American Society of Addiction Medicine (ASAM) meeting, featuring workshops for ASAM attendees and opportunities for NIDA research dissemination and continuing medical education credits.

Item

Education. - The Committee encourages NIDA to continue its work in the area of education to inform people of all ages of the detriment to society that drug abuse causes in terms of pronounced effects on health and the extensive expense to the economy of the Nation. (p. 103)

Action taken or to be taken

NIDA recognizes the critical importance of providing accurate and compelling scientific information about drug abuse to all members of society, particularly our Nation's youth, since that is when drug experimentation usually begins. For example, NIDA funds a small grants program - the Science Education Drug Abuse Partnership Awards - to support innovative product development to enhance knowledge and understanding of neuroscience and the biology of drug abuse and addiction among students, college aged youth, journalists, legislators, and others. Products range from award-winning websites offering science education games and curriculum materials for middle school students and teachers (<http://reconstructors.rice.edu>) to the Addiction Studies Institute for Journalists, which supports national workshops on topics related to drug abuse. NIDA also has the lead on a new Neuroscience Blueprint initiative to improve neuroscience education in grades K-12. Eight investigators across the United States have received funding to develop different programs (e.g., a clinical trials role-play game and a mobile neuroscience exhibit that will travel to underserved areas).

In addition, NIDA continues its active outreach to young people as well as other members of society with actionable information about drugs. Several examples follow:

National Drug Facts Week (NDFW). NDFW is a health observance week targeting teens and aimed at shattering common myths about drugs. In 2010, close to 100 events were held in 23 states, more than 250,000 teens received NIDA's new booklet for teens titled *Drugs: Shatter the Myths*, and more than 12,000 people took NIDA's online quiz, "The National Drug IQ Challenge". NIDA also held the first *MusiCares and GRAMMY Foundation's Teen Substance Abuse Awareness through Music Contest*. In its second year, NDFW continues to foster community partnerships among scientific experts, teens, and Federal and private-sector organizations and provide web-based materials for use in designing and hosting local events.

NIDA for Teens Website. NIDA has expanded this highly successful website, recently adding a *PEERx* (<http://teens.drugabuse.gov/peerx/choose-your-path/>) educational tool to provide teens with information about prescription drug abuse and to encourage them to interact with other teens in a positive way. NIDA is partnering with several organizations, including Students Against Destructive Decisions, to inform site content and help ensure that it speaks to teens. NIDA continues to provide regular updates to the highly successful Sara Bellum Blog and to

respond to posted comments from its mainly teen audience. The interactivity of these sites underlies their success, as numbers of visits to the website exceed half a million every month.

Website for Adults with Low Literacy. NIDA is in the final stages of developing a website, specifically for low-literacy adults, to share information about drug abuse science, prevention, and treatment. The website includes personal stories and information on various drugs and where to get treatment information. To ensure its use by the intended audience, the website was developed with input from literacy educators, health care providers, faith and community groups, and others having contact with low-literacy adults; these partnerships that will continue throughout dissemination. Once released, the website will be accessible through both NIDA's homepage and a unique web address.

Item

Medications Development. - The Committee encourages NIDA to use all available mechanisms, including the Small Business Innovation in Research program, to expand support for medications development to treat diseases of drug abuse and addiction. (p. 103)

Action taken or to be taken

Drug abuse and addiction exact an exorbitant toll on affected individuals, their families, and the societies in which they live. Despite this enormous burden, few medications are yet approved to treat substance abuse disorders. This disconnect - together with enduring stigma and reluctance by the pharmaceutical industry to invest in addiction research - has made the development of addiction medications a top priority for NIDA. Therefore, as the Committee suggests, NIDA is using all available mechanisms to advance the development of addiction medications.

One mechanism is NIDA's Small Business Innovation Research (SBIR) program with its goal of stimulating technological innovation by supporting research with commercialization potential. This year (May 2011) NIDA released a Notice in the *NIH Guide for Grants and Contracts Updates* to underscore the high programmatic priority given to research that seeks to promote medications discovery and development-enabling activities. Included would be research to advance innovative genotyping and sequencing platform technologies, which will aid the development of more targeted substance abuse interventions based on genetics screening for tobacco dependence and treatment, for example.

An exemplary SBIR project is developing a nasal spray for the emergency treatment of opioid overdose. In 2008, there were almost 15,000 overdose deaths in the U.S. involving prescription and illicit opioids. The medication being developed could help prevent fatal drug overdoses by blocking the respiratory depression that opioids cause.

To further spur advances in medications development, in 2010 NIDA began offering Translational Medications Avant-Garde Awards to support bold and highly innovative research approaches. NIDA's 2011 awards produced two grants, both focused on vaccines: one to hasten development of a methamphetamine vaccine and the other to test a nicotine vaccine that may be less costly with fewer side effects than those currently in development. Since no FDA-approved medications exist for methamphetamine addiction, a vaccine could have a major impact.

Vaccines are also being tested for cocaine and heroin, with complementary research to develop better adjuvants (substances that enhance the immune response) for greater vaccine efficacy.

Another new strategy is represented in novel public-private partnerships to develop, test, and facilitate the distribution of safe and effective anti-smoking medications. The goal is to leverage the strengths and resources of public, nonprofit, and private-sector entities to accelerate medications development at reasonable costs. In September 2011, NIDA made three awards for the developmental phase of this initiative intended to assess the scientific opportunities in anti-smoking drug development, to study the feasibility of founding a public-private partnership, and to present a strategic business plan for moving forward. In 2012, NIDA will award the second phase of this initiative to a single group who will apply the proposed developmental research plan, scientific approaches, and evaluation tools from the planning phase to a large PDP execution phase. This approach will help ensure a constant flow of compounds that can progress from “molecule to medicine” at a more rapid pace.

Finally, recent grantees in NIDA’s Medications Development Centers of Excellence program are evaluating novel medication combinations for “hard to treat” populations, such as those dependent on cocaine and alcohol.

Item

Military Personnel, Veterans, and Their Families. - The Committee commends NIDA for its successful efforts to coordinate and support research with the Department of Veterans Affairs and other NIH institutes on substance abuse and associated problems among U.S. military personnel, veterans and their families. Many military personnel need help confronting war-related problems including traumatic brain injury, post-traumatic stress disorder, depression, anxiety, sleep disturbances, and substance abuse, including tobacco, alcohol and other drugs. Many of these problems are interconnected and contribute to individual health and family relationship crises, yet there has been little research on how to prevent and treat the unique characteristics of wartime-related substance abuse issues. The Committee commends NIDA for this crucial work. (p. 103)

Action taken or to be taken

As the White House’s Office of National Drug Control Policy reported in February 2010, analyses of U.S. Department of Defense surveys among military and active duty military personnel show a sharp uptick in drug abuse, driven largely by the nonmedical use of prescription drugs. Problems with alcohol and nicotine are also highly prevalent and pose significant health risks to active, reserve, and guard military personnel. Certain mental health disorders, such as post-traumatic stress disorder (PTSD), are also overrepresented, and suicide risk is a major concern.

NIDA, together with NCI, NIAAA, and the U.S. Department of Veterans Affairs (VA), issued a multi-agency funding opportunity in 2010 to enhance and accelerate research on prevention and treatment of alcohol, tobacco, and other drug use, as well as associated mental health problems among members of the military (active duty and recently separated from the military) and their families. This call for research, which resulted in \$6 million in grants (\$4 million from the NIH,

\$2 million from the VA), will help fill research gaps in understanding the problems faced by military personnel serving or having served in Operation Enduring Freedom (Afghanistan) or Operation Iraqi Freedom (Iraq) and their families.

Areas to be addressed by some of these funded grants include (1) use and abuse of prescription opioids among combat veterans; (2) veterans' treatment-seeking patterns (how and why they do or do not seek out treatment); (3) integration and testing of treatments for the interrelated problems facing returning military personnel, including depression, anxiety, sleep disturbances, and substance abuse; (4) effectiveness of a web-enhanced parenting program for military families; and (5) analysis of perceptions about military members' tobacco use, as well as barriers and facilitators to military tobacco control policy.

In addition, NIMH and the U.S. Army are jointly supporting a study of risk factors related to suicide among Army soldiers titled the Army Study to Assess Risk and Resilience in Service members (Army STARRS) (<http://www.armystarrs.org/>). This study is the largest ever conducted on mental health risk and resilience among military personnel. Since the study began in 2009, investigators have collected survey data from more than 25,000 soldiers.

The aim of this research agenda is to learn more about the factors that increase or reduce risk of substance abuse and mental health problems, inform educational outreach initiatives to decrease tobacco use among military personnel, and increase understanding of suicide risk and prevention in the Army. This research should help determine the potential for existing evidence-based prevention interventions and services for substance abuse, whether alone or with services for other comorbid conditions, to address the range of substance abuse and other psychological challenges that arise across the deployment cycle for military personnel, veterans, and their families.

Item

Prescription Drug Abuse. - The Committee applauds the Committee for its continued effort to halt prescription drug abuse. This effort requires the cooperation of many components of the Federal Government, but NIDA should maintain its comprehensive leadership role in this important area. (p. 103-104)

Action taken or to be taken

The nonmedical use and abuse of prescription drugs is a serious public health problem in this country - evidenced by the number of unintentional overdose deaths involving opioid pain relievers, which have quadrupled since 1999, outnumbering those involving heroin and cocaine. Young adults aged 18 to 25 have the highest rates of abuse, and teens are of special concern because of the more severe consequences, including addiction, that stem from early abuse of all drugs. According to the 2010 Monitoring the Future Survey, eight percent of 12th graders reported past-year nonmedical use of the prescription opioid Vicodin, which retains its status across six years as one of the most commonly abused drugs by high school seniors. And while teen abuse of most illicit drugs, alcohol, and cigarettes has declined considerably over the past decade or so, abuse of prescription drugs has not.

The high prevalence rates of prescription drug abuse likely result from multiple factors, including (1) the mistaken belief that prescription drugs are safe, even for nonmedical reasons, and (2) their increasing availability in our society. For example, between 1991 and 2010, prescriptions for stimulants increased from five million to nearly 45 million, a nine-fold increase over 20 years; similarly prescriptions for opioid pain relievers increased from about 75 million to almost 210 million, nearly tripling in this time period.

In response, NIDA is working with the Office of the Surgeon General and other Federal agencies to raise awareness and engage numerous stakeholders to take action on this urgent problem. A resulting Surgeon General response (*Call to Action*) is expected to be published in spring 2012 and will address both adolescent and young adult motivations for abuse, environmental influences in the culture at large, and other factors such as drug sharing by friends and family members, which may be helping to fuel this epidemic. More broadly, the NIDA Director co-chairs a subcommittee of the HHS Behavioral Health Coordinating Committee devoted to addressing prescription drug abuse. NIDA is also involved in the implementation of the White House Office of National Drug Control Policy's 2011 Prescription Drug Abuse Prevention Plan.

Prevention, education, and outreach are critical in curbing prescription drug abuse. In that regard, NIDA is using the NIDAMED initiative to encourage physician screening of their patients for tobacco, alcohol, and illicit and prescription drug abuse, and is providing training to medical students and residents. NIDA has also taken the lead at NIH to develop educational curriculum for medical students, nurses, and dentists on how to screen pain patients, properly prescribe analgesics, and prescribe in ways that minimize the likelihood of diversion and abuse. NIDA is reaching out to teens with a new initiative known as PEERx, providing factual information about the harmful effects of prescription drug abuse on the brain and body.

Finally, NIDA is supporting research on alternative pain relievers (new molecules, delivery systems, or combinations) that make drug use less rewarding and thus less likely to produce addiction. NIDA also continues to fund research to better understand the factors that predispose someone to become addicted to prescription pain relievers, and what can be done to prevent it among those at risk. This is timely, given the growing elderly population and the many returning injured veterans.

Item

Substance Abuse by Teenagers. - The Committee urges NIDA to concentrate its effort to reverse the recent increase in experimentation in substance abuse by teenagers. This effort will require innovative approaches in the education, prevention and treatment arenas. (p. 104)

Action taken or to be taken

Following a decade of steady declines, adolescent substance abuse may be on the rise. For example, according to the 2010 Monitoring the Future Survey, there not only have been increases in past year and past month marijuana use by 8th graders, but there has also been an increase in daily marijuana use for 8th, 10th, and 12th graders - a serious harbinger of problems to come. NIDA takes a necessarily multi-pronged approach - from basic and clinical neuroscience

to prevention, treatment, education, and outreach (see Education, p.110) - to address this problem.

Preventing drug use among youth remains an important public health issue, as early drug use is an important predictor of more serious substance use problems later in life. In addition to the development and testing of prevention interventions, NIDA continues to support research to identify risk and protective factors that can be modified to prevent drug use initiation. For example, a recent study that followed a cohort of 1,000 children from birth found that those who showed poor childhood self-control - as early as age 3 - were more likely to have problems with physical health, substance dependence, and personal finances, and to be convicted of a criminal offense by 32 years of age, regardless of intelligence and socioeconomic status. Interestingly, while some of these outcomes were the result of mistakes made during adolescence (e.g., starting smoking, dropping out of high school, becoming parents), poor self-control in childhood was still predictive of problems in adulthood. even in those adolescents who did not make the same mistakes. Therefore, early childhood interventions that enhance self-control have the potential to have a greater impact than addressing problem behaviors in adolescence alone.

While research on evidence-based prevention interventions has shown potential to reduce risk factors and promote positive development in youth, substantial challenges are faced when implementing these interventions within communities. Thus systems for increasing use of these programs in communities are needed. Two systems-level interventions, Communities that Care and PROSPER, can help communities identify substance abuse prevention needs and implement evidence-based preventive interventions to address them community-wide. Both interventions have demonstrated reductions in substance abuse years after program implementation. To help shrink the gap in translating prevention science to practice and significantly improve the public health impact of prevention programs across communities, NIDA continues to make implementation science a high priority.

On the treatment front, advances in research on adolescent brain development have shown that the brain continues to develop into early adulthood; these maturational changes not only influence substance use initiation and progression, but also the brain processes that may be targeted in treatment. In 2010, NIDA solicited research applications and funded three studies to integrate findings from research on brain development, cognition, and neuroscience into the development of innovative and effective, developmentally sensitive drug abuse treatments for adolescents.

Item

Translational Research. - The Committee recognizes the value of the translational research funded by NIDA, which includes preventive and treatment modalities directed toward a decrease in drug experimentation and most importantly the development of treatments for the diseases of drug dependence. (p. 104)

Action taken or to be taken

For much of the 20th century, people viewed addiction as a moral failing, a lack of willpower. No one knew that drugs of abuse could actually change the structure and function of the brain,

eroding the very circuits necessary for exerting control over behavior. Today, thanks to NIDA-supported research, we know how drugs of abuse act in the brain and which circuits they target to drive the compulsive behaviors in addiction. These discoveries have expanded the array of pharmacological and behavioral strategies for targeting brain regions common to multiple addictions (e.g., to dampen stress reactivity, to inhibit conditioning, and to improve control over behavior).

Knowledge gained from genetics research is also revealing new molecular targets for addiction medications. A compelling example is the alpha 5 nicotinic receptor, recently linked to nicotine dependence, withdrawal, and tobacco-related illness. Preclinical studies reveal the value of alpha 5 as a potential target for treatment, not just of nicotine addiction but also for other drugs.

To stimulate the pursuit of addiction medications, NIDA launched a Translational Avant-Garde Award to help researchers realize the therapeutic potential of their scientific discoveries and accelerate their development (see Medications Development, p.111). One Avant-Garde team is pursuing a medication for nicotine addiction using a novel approach that targets the endogenous cannabinoid system. They will identify and optimize compounds that inhibit an enzyme called fatty acid amide hydrolase (FAAH), shown in animal studies to reduce nicotine self-administration and prevent nicotine-induced reinstatement. Such findings could be the basis for greater pharmaceutical industry involvement, particularly with smoking cessation therapies.

Equally important to basic science discoveries is ensuring that proven prevention and treatment interventions reach their intended audiences: Prevention Implementation Science, designed to move interventions into communities, is therefore an important focus area for NIDA. It is also important to ensure that evidence-based treatments make their way into community programs and other venues where they are urgently needed. To this end, NIDA's Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) program continues to foster partnerships with public health and public safety agencies and a host of drug treatment, criminal justice, and health and social service professionals to test evidence-based treatments in criminal justice settings. CJ-DATS currently is testing a protocol on medication-assisted treatment for opioid addiction to improve linkages between correctional supervision (e.g., parole/probation officers) and community providers. In the area of HIV, a priority in NIDA's translational portfolio is the implementation and sustainability of "Seek, Test, Treat, and Retain," which aims to link HIV+ substance abusers with highly active antiretroviral treatment (HAART) and follow them in care. Substance abusers are at greater risk of HIV infection and yet much less likely to be treated if they contract HIV. Since it is now recognized that early HAART treatment not only improves outcomes in patients but also prevents the transmission HIV, NIDA is supporting implementation research in the criminal justice system, substance abuse treatment programs, and the healthcare community.

NIDA's Drug Abuse Treatment Clinical Trials Network, now over a decade old, continues to test treatments in real-world settings, elicit feedback on their success and feasibility, and develop implementation tools for research-based practices. Working with others to get this knowledge into the hands of treatment professionals is a key component of the change NIDA is striving to bring about in drug abuse treatment (see Blending Initiative, p.109).

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Senate Significant Items

Item

Underage Drinking Initiatives. - The Committee applauds NIAAA's continued focus on underage alcohol use and college binge drinking research. The Committee urges NIAAA to continue research to evaluate campus-based programs that seek to reduce drinking and related problems among college students using both individual and environmental approaches, including mandated intervention and/or treatment and community partnerships that involve heavy publicity and highly visible enforcement. The Committee recognizes the critical role of psychological research in understanding drinking behavior and in developing behaviorally based interventions as well as the demonstrated effectiveness of those interventions alone or in combination with pharmacotherapy. (p. 102-103)

Action taken or to be taken

For over a decade, NIAAA has invested substantial resources in addressing college drinking, supporting research on interventions at both the individual and environmental levels. At the individual level, research has shown that screening and brief intervention in the college student health center can be effective in reducing high risk drinking and alcohol-related consequences. At the environmental level, a recently completed large scale clinical trial showed the effectiveness of community college partnerships in reducing alcohol problems in off campus settings through the implementation of heavily publicized and highly visible alcohol policy and enforcement activities. Finally, an evaluation of an online alcohol education course for incoming freshman showed benefits through the first semester in reducing binge drinking and alcohol-related problems. These results highlight opportunities to intervene with problem drinking and its associated consequences at different levels and time points during college and suggest that combining prevention strategies may be especially effective. In 2011, NIAAA established a College Presidents Working Group to bring national attention to the college drinking issue. Together with extramural scientists and the Working Group, NIAAA is creating a “matrix” of college interventions organized by effectiveness, cost, and ease of implementation that college administrators may use as a guide for developing and implementing interventions on their campuses.

National surveys indicate that most students have experience with alcohol before entering college, underscoring the need to address underage drinking in children and adolescents and preempt future problems. To encourage alcohol screening of youth ages 9-18, NIAAA recently released a developmentally-appropriate, empirically-based two-question alcohol screener and risk estimator that provides a quick, user-friendly way for clinicians to screen and provide brief interventions to young patients.

Although behavioral interventions have demonstrated efficacy with youth in treatment, more than half relapse within six months. Medications and behavioral therapy together may improve outcomes, but little is known about their effectiveness in young people. NIAAA will continue to support research on the effectiveness and developmental appropriateness of various treatment approaches in youth. Recognizing the importance of psychological research in developing

improved intervention strategies in all venues, NIAAA's Acting Director participates in the HHS Behavioral Health Coordinating Committee and co-chairs the Subcommittee on Alcohol Policy and Underage Drinking.

National Institute of Nursing Research (NINR)

Senate Significant Items

Item

Science-Driven Practice. - The Committee supports NINR's efforts to prepare faculty researchers, who are desperately needed to educate new nurses. NINR's continued commitment to the science-driven practice of the nursing profession remains vital to preventing disease, improving quality patient care, and ensuring the proper training and development of nurse researchers. (p. 102)

Action taken or to be taken

The National Institute of Nursing Research (NINR) improves the Nation's health by building the evidence base for successful health promotion and disease prevention programs, well-informed person-centered healthcare decisions, innovative technologies that support clinical care and accelerate scientific discovery, and by supporting new investigators and cutting edge, transformative ideas and approaches. NINR focuses on health and illness across the life span to build the scientific foundation for clinical practice, prevent disease and disability, manage and eliminate symptoms caused by illness, and improve palliative and end-of-life care.

Over the past 25 years, NINR has developed a strong infrastructure for nursing research and built a dynamic, vital, and productive community of investigators dedicated to conducting the research that establishes the scientific basis for patient care. A critical component of this infrastructure, the support and development of the next generation of nurse scientists, will continue through NINR's training activities, designed to achieve the vision of an innovative, multidisciplinary, and diverse scientific workforce. For example, in addition to supporting pre- and post-doctoral research fellowships and career development awards in the extramural community, NINR recently solicited applications for a new initiative known as the Scholars Training for the Advancement of Research, or STAR, program. This innovative program provides additional resources for institutions with existing NINR-supported training programs to support the interdisciplinary "fast-track" training of outstanding students finishing baccalaureate degrees in nursing who are interested in pursuing a PhD in research. NINR also supports investigators under the NIH K99/R00 Pathway to Independence (PI) program, in which promising postdoctoral scientists receive both mentored and independent research support for up to five years. NINR is also actively engaged in developing the next generation of researchers through activities in its Intramural Research Program such as the Summer Genetics Institute, Graduate Partnerships Program, and Methodologies Boot Camp. Many of these scientists will go on to become the nursing faculty researchers urgently needed to maintain a nursing workforce focused on evidence-based practice.

Efforts such as the NINR Centers Program will also continue supporting the training and career development of nurse scientists, while promoting the adoption of evidence-based research into practice. Across the United States, NINR-supported research Centers function as translational research hubs within schools of nursing, designed to speed the application of research into practice. Facilitating collaboration between disciplines and across institutions through the use of shared resources and expertise, the Centers: increase research capacity; enhance the mentorship

of doctoral students and early-career scientists; and expand the scientific reach of investigators working on multiple projects.

National Institute on Minority Health and Health Disparities (NIMHD)

Senate Significant Items

Item

Diabetes. - The Committee urges NIMHD to expand, intensify and support ongoing research and other activities with respect to pre-diabetes and diabetes, particularly type 2 diabetes, in minority populations, including research to identify clinical, socioeconomic, geographical, cultural and organizational factors that contribute to diabetes in such populations. Specifically, the Committee encourages the Institute to support research on behavior and obesity; environmental factors that may contribute to the increase in type 2 diabetes in minorities; environmental triggers and genetic interactions that lead to the development of type 2 diabetes in minority newborns; genes that may predispose individuals to the onset of type 1 and type 2 diabetes and its complications; methods and alternative therapies to control blood glucose; and diabetic and gestational diabetic pregnancies in minority mothers. The Committee also asks that NIH, through NIMHD and the National Diabetes Education Program, mentor health professionals to be more involved in weight counseling, obesity research and nutrition; provide for the participation of minority health professionals in diabetes focused research programs; and encourage increased minority representation in diabetes focused health fields. (p. 106)

Action taken or to be taken

Research on diabetes in minority populations is a significant part of the NIMHD's health disparities research portfolio. NIMHD is supporting ongoing research on the socioeconomic, geographical, cultural, and environmental factors contributing to diabetes rates in racial and ethnic minorities. For example, a project funded under the NIMHD Faith-Based Initiative examines high rates of diabetes among Pacific Islanders in the U.S. Associated Pacific Islands - Commonwealth of the Northern Mariana Islands (CNMI) and in the State of Hawai'i. The research addresses the social-cultural constructs and incorporates a faith-based and community intervention to reduce diabetes rates and its complications in these communities. Furthermore, the NIMHD Centers of Excellence are conducting research exploring genetic risk factors for metabolic syndrome in racial/ethnic minority populations, diabetes self management models, and the use of traditional healing practices in preventing diabetes and its complications. The Environmental Health Disparities Initiative represents a collection of institutions under cooperative agreements to support research projects in existing NIMHD Centers of Excellence focusing on social and environmental determinants of health to reduce health disparities in minority populations. A key objective is to support research projects that would integrate and elucidate the complex interactions of environmental, social, behavioral, and biological factors and policies as they relate to health disparities including diabetes and obesity in racial and ethnic minority populations.

In addition, NIMHD funds health disparities research focused on diabetes through the investigator-initiated research grants program using the R01 funding mechanism. For example, the Understanding Health Disparities in the Progression of Type 2 Diabetes project involves the adaptation of a stress management intervention to be delivered by community health workers to urban Latinos with Type 2 diabetes. The intervention will test the impact of stress management training on glycemic control as well as on stress hormones, psychosocial functioning, and stress-

glucose reactivity. The NIMHD Community-Based Participatory Research (CBPR) Initiative has engaged faith-based organizations, community health workers, and other community stakeholders to develop and implement behavioral interventions that encourage the adoption of healthy lifestyles to address pre-diabetes and diabetes. For example, one project utilizes trained lay health educators who are members of the community to deliver guided discussions regarding diabetes to family members and friends.

In addition, NIMHD is actively represented on the NIH Diabetes Mellitus Interagency Coordinating Committee and participated in the development of the Strategic Plan. The NIH Health Disparities Strategic Plan and Budget is also a mechanism that will continue to allow NIMHD to foster research collaborations with the Institutes and Centers at NIH to address diabetes in racial and ethnic populations. Engaging future researchers and health professionals in diabetes focused research is a priority for NIMHD. Training and mentoring of diverse health professionals is made possible through the NIMHD Loan Repayment Programs and the NIMHD Disparities Research and Education Advancing our Mission (DREAM) Career Transition Awards. NIMHD LRPs are part of the extramural program and DREAM is part of the Intramural Research Program. Moreover, as a complement to our mission, NIMHD will further engage with the National Diabetes Education Program (NDEP), which has taken a multicultural approach to address its goals of improving diabetes prevention, management, treatment, and outcomes for populations disproportionately affected by diabetes, including racial and ethnic minorities.

Item

Glomerular Diseases. - The Committee notes that African Americans are five times more likely to develop glomerular diseases, such as focal segmental glomerulosclerosis [FSGS], than Caucasians. The Committee urges NIMHD to collaborate with NIDDK on this important issue. (p. 106)

Action taken or to be taken

Glomerular disease remains a focus of the National Institute on Minority Health and Health Disparities (NIMHD) research agenda through the Centers of Excellence Program, which supports biomedical, clinical, behavioral, and community-based participatory research; research training; and community outreach in minority health and health disparities. For example, the Comprehensive Research Center in Health Disparities at the University of California-San Diego has been investigating the progression of end-stage renal disease (ESRD) in African Americans with a particular interest in the genetic risk factors for ESRD and the role of the sympathetic nervous system in the progression of kidney disease.

Moreover, in 2010, NIMHD co-sponsored a conference convened by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on the potential biological and social impact of the discovery of genetic variations that appear to predispose African Americans to certain forms of kidney disease, including focal segmental glomerulosclerosis (FSGS). Staff from NIDDK, NIMHD, and other NIH Institutes and Centers reviewed genetic, public health, ethical, and social implications of these new findings, and conference participants provided feedback to NIH regarding potential future research directions. After the conference, NIMHD met with officials from the NephCure Foundation to discuss these important health disparities

conditions. Subsequently, glomerular disease, including FSGS, is now identified as a priority research area in NIMHD funding opportunity announcements. NIDDK-supported researchers have recently identified a strong association between the circulating factor suPAR and both primary and recurrent FSGS, suggesting that this factor could be a target for new FSGS prevention or treatment approaches. NIDDK, NIMHD, and other NIH components continue to build on this and other collaborations and shared interests to better understand and address the high prevalence of FSGS in African Americans.

Item

Obesity. - The Committee strongly urges NIH to continue to support research to identify and reduce health disparities, including studies focusing on populations at disproportionate risk for obesity and its accompanying health consequences such as, but not limited to, cancer, diabetes and cardiovascular disease. To effectively address the problem of obesity and its health consequences, the Committee requests that NIMHD intensify its investment in obesity research and review the benefits of establishing a Comprehensive Center of Excellence for Obesity Research and Prevention. Further, the Committee urges NIH to develop a trans-NIH strategy for obesity research that is coordinated and has a significant health disparity obesity research focus coordinated through NIMHD. This comprehensive approach will critically and systematically explore the causes and potential solutions for health disparities in obesity. Studies should focus on regions with populations at disproportionate risk for obesity and its health consequences, in particular populations most affected racial and ethnic minorities, low-income populations and rural populations and include regional analysis. The Committee requests NIH to participate in a trans-HHS working group that sets measurable objectives based on scientific data and information that leverages the appropriate HHS agencies like AHRQ and CDC in order to improve dissemination and implementation of scientific information to clinicians and community organizations to aggressively improve obesity rates in health disparate populations. (p. 106)

Action taken or to be taken

In response to the obesity epidemic, the NIH Obesity Research Task Force was established to accelerate progress in obesity research across NIH. The NIH Obesity Research Task Force published an updated *Strategic Plan for NIH Obesity Research* in 2011. NIMHD is actively represented on the NIH Obesity Research Task Force and participated in the development of the trans-NIH Strategy for Obesity Research. The new *Strategic Plan* emphasizes research to reduce health disparities as essential to all areas of obesity research. NIH supports many studies that include disproportionately affected racial and ethnic groups and socioeconomically disadvantaged populations. For example, the Diabetes Prevention Program (DPP), led by NIDDK, showed that type 2 diabetes prevention is possible in people of diverse racial and ethnic groups who are overweight/obese and have pre-diabetes, through lifestyle or medical intervention. Moreover, pursuant to the NIH Health Disparities Strategic Plan and Budget, NIMHD collaborates, coordinates, and reviews minority health and health disparities research and other activities at NIH, which includes health disparities research on obesity conducted by NIDDK, NHGRI, NICHD, and NHLBI.

In order to address the problem of obesity and its health consequences in racial and ethnic minority communities, NIMHD has supported research through its Centers of Excellence (COE)

Program and the Community-Based Participatory Research (CBPR) Initiative that focused on the social, economic, geographic, and cultural roots of obesity as well as maternal and child health, prevention, and physical activity. NIHMD COEs continue to be engaged in research on diabetes and obesity, including some of the co-morbid conditions and diseases often associated with obesity, diabetes, or both. In addition to basic research, several are also conducting interventions. For example, a COE is exploring the connection between diabetes control and cognitive decline. The COE has recently reported that a telemedicine intervention, initiated by a home visit by a diabetes nurse and that included 5 annual follow-up visits, resulted in cognitive improvements and in improvements in HbA1c, but not systolic blood pressure or low density cholesterol. To better understand the dietary behaviors of diabetics, COE researchers have recently developed and validated the Latino Dietary Behaviors Questionnaire (LDBQ) for measuring the dietary behaviors of low-income, Spanish Caribbean Latinos with type 2 diabetes. Moreover, COE researchers have analyzed associations between insulin resistance and other markers of disease in a sample of Mexican American adolescents from a severely disadvantaged community on the Texas-Mexico border. This study found that approximately 50% of their sample (mean age, 16 y) were overweight or obese, and more participants were obese than overweight. Participants (27%) in this sample had insulin resistance, a potent predictor of diabetes, and two biomarkers, low high-density lipoprotein cholesterol and high waist circumference, that were strongly linked to insulin resistance.

The NIMHD CBPR Initiative portfolio supports a number of research projects that directly address obesity. One project aims to increase healthy eating, physical activity, and physical fitness among adolescents by implementing a school-based CBPR intervention that seeks to improve the school food environment, promote physical activity, and empower adolescents to advocate for changes in their community. The findings from this project and advocacy by community partners were instrumental in getting legislation passed in California to provide free, fresh drinking water during school meal times, which emerging studies suggest could prevent adolescent obesity. Recognizing the opportunity to build upon the obesity portfolio and the work conducted at COEs, NIMHD continues to include obesity as a research area of interest and would encourage applications from any academic institution interested in establishing a Comprehensive Center of Excellence for Obesity Research and Prevention.

Item

Scleroderma. - The Committee commends the Institute for establishing the Exploratory Centers of Excellence Program and is pleased that health disparities research related to scleroderma will be prioritized. (p. 107)

Action taken or to be taken

The National Institutes on Minority Health and Health Disparities (NIMHD) Centers of Excellence Program represents a scientific platform to conduct biomedical, clinical, behavioral, and community-based participatory research; research training; and community outreach in minority health and health disparities. NIMHD recognizes that understanding disease etiologies and variations in genetic susceptibilities among racial and ethnic minorities will be necessary to reveal their roles in the wider spectrum of factors contributing to health disparities. Studies have shown that genomic variants can contribute to heightened susceptibility and development of

autoimmune diseases such as scleroderma. Recognizing the need to address health disparities research related to diseases such as scleroderma, NIMHD continues to identify scleroderma as a priority research area in NIMHD funding opportunity announcements (FOA).

Pursuant to its responsibilities to plan, collaborate, coordinate, review, and evaluate minority health and health disparities research and other activities at NIH and to coordinate development of the NIH Health Disparities Strategic Plan and Budget, NIMHD will build upon its relationships with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the other Institutes and Centers to better understand and address health disparities research related to scleroderma.

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National Center for Complimentary and Alternative Medicine (NCCAM)

Senate Significant Items

Item

Access to Natural Product Collections. - The Committee supports the efforts of NCCAM to increase its access to comprehensive and professionally organized natural product libraries, as such collections represent valuable research resources to facilitate the efficiency and cost-effectiveness of the Center's research program. (p. 105)

Action taken or to be taken

The National Center for Complementary and Alternative Medicine (NCCAM) appreciates the Committee's support of its efforts to facilitate open access to researchers of a large, well characterized natural products library. Advancing research on natural products was identified as a priority area for NCCAM as part of a thorough strategic planning process conducted in 2010 that included extensive input from the Center's stakeholders. Currently, NCCAM is exploring opportunities to partner with other NIH Institutes and Centers, academic and non-profit institutions, and industry to provide researchers access to a natural products library. As part of that effort, a recent National Advisory Council for Complementary and Alternative Medicine meeting included a symposium on natural product screening. Several scientists with expertise in natural product screening and chemistry presented, including a scientist from a pharmaceutical company.

Additionally, NCCAM is funding two investigators to screen a natural product library for compounds that may lead to the development of new drugs and/or advance our understanding of the mechanism of action of specific natural products. If the results from these initial studies are promising, NCCAM may issue a funding opportunity announcement for researchers to conduct more extensive screening of the natural products library.

Item

Behavioral Interventions. - The Committee commends NCCAM's support of research on the cognitive and emotional effects of mindfulness meditation, and it encourages the Center to collaborate with other institutes and centers to explore additional behavioral interventions. (p. 105)

Action taken or to be taken

The study of the effects of mindfulness meditation is an area of special interest to the National Center for Complementary and Alternative Medicine (NCCAM). Advancing research on mind and body interventions, practices, and disciplines was identified as a priority area for NCCAM as part of a thorough strategic planning process conducted in 2010 that included extensive input from the Center's stakeholders. Meditation has been used for centuries to increase calmness and physical relaxation, improve psychological balance, cope with illness, and enhance overall health and well being. Research on meditation has demonstrated that it is a very powerful tool for learning, controlling attention, and regulating emotion, and it may reduce symptoms of anxiety, depression, and chronic pain. For example, the results from an NCCAM-funded study published

in 2011 demonstrated that practicing mindfulness meditation appears to be associated with measurable structural changes in the brain regions involved in memory, learning, and emotion. Going forward, NCCAM will continue to support and encourage research in this scientifically promising area.

Additionally, NCCAM is collaborating with other NIH Institutes and Centers (ICs) to support larger NIH efforts on behavioral research. Specifically, NCCAM participates in several trans-NIH working groups, supports Funding Opportunity Announcements (FOAs) with other ICs, and cosponsors workshops and seminars. Examples of the trans-NIH working groups that NCCAM participates in are the NIH Blueprint for Neuroscience Research, the NIH Basic Behavioral and Social Sciences Opportunity Network (OppNet), and the NIH Pain Consortium, each of which includes a focus on research on behavioral interventions.

NCCAM also cosponsors FOAs with other ICs to leverage the Center's investment in behavioral research. For example, NCCAM participated in an OppNet initiative cosponsored by multiple ICs to fund research investigating the basic psychological, social and environmental mechanisms and processes linking psychosocial stressors and behavior. Another FOA co-supported by NCCAM is a National Institute of Nursing Research initiative to sponsor innovative research to identify mechanisms that influence or promote positive sustainable health behaviors in children and youth. Over the past year, NCCAM has also joined many other ICs in supporting an FOA issued by the Office of Behavioral and Social Sciences Research to translate findings from basic research on human behavior into effective clinical, community, or population-based behavioral interventions to improve health. Additionally, NCCAM participated in a recent FOA issued by the National Human Genome Research Institute to support Small Business Innovative Research Grants to develop new technologies to study biology and behavior from basic and clinical perspectives. NCCAM also joined the National Cancer Institute in issuing an FOA to support research on behavioral interventions related to cancer prevention, treatment, survivorship and end-of-life issues.

National Center for Advancing Translational Sciences (NCATS)

Senate Significant Items

Item

Behavioral Research. - The Committee encourages NCATS to include staff expertise and resources to manage research on the translation of behavioral interventions into communities. (p. 108)

Action taken or to be taken

In pursuit of its mission to catalyze the generation of innovative methods and technologies for enhancing the development, testing, and implementation of diagnostics and therapeutics, NCATS will support the full spectrum of translational research, including research on the translation of behavioral interventions into communities. As such, NIH has transferred staff with broad experience and expertise in the area of outreach into communities to the NCATS in order to ensure the effective management of resources for research on the translation of behavioral interventions into communities.

Item

Clinical and Translational Science Awards [CTSAs]. - The Committee is encouraged by the success of the CTSA consortium and strongly recommends that the program be fully funded, consistent with professional judgment, as it nears full implementation. As the CTSA program transitions to NCATS, the Committee urges the NIH Director to ensure that the current focus on the full spectrum of translational research is maintained. The inclusion of patient centered outcomes research, community engagement, training, dissemination science, and behavioral research is extremely important to the translation and application of basic science discoveries and success of the CTSAs. (p. 108)

Action taken or to be taken

NIH recognizes that the CTSAs have broad experience and expertise in the full spectrum of translational research, including patient centered outcomes research, community engagement, training, dissemination science, and behavioral research. This breadth and diversity is considered to be an important asset of the program that will continue to be supported at NCATS.

Item

Drug Repurposing. - There are over 11,000 commercial compounds that are in a pool of late-stage, pre-clinical through phase III clinical trials that have been tested in humans, but whose development has been discontinued by pharmaceutical companies. By leveraging existing compounds, researchers and industry can develop new treatments for patients. The Committee encourages NIH to work with pharmaceutical companies to support drug repurposing and the sharing of compounds; in particular, NIH is encouraged to develop guidelines for drug repurposing technology transfer agreements. (p. 108)

Action taken or to be taken

On average, developing a new drug takes 15 years and costs nearly a billion dollars. Repositioning drugs that have not been approved (drug rescue) and drugs that are already approved (drug repurposing) has been broadly accepted as a valuable mechanism to develop therapeutic approaches for new indications more efficiently, more rapidly, and at a lower cost than the research and de novo development required for novel compounds. A significant advantage offered by drug rescue and repurposing efforts stems from the fact that all approved drugs and many abandoned compounds have been tested in humans. The data from such studies provides detailed information regarding dosing, pharmacology, and toxicity. Building on this prior information, clinical trials for new indications can be initiated more quickly and economically.

While the private sector holds many of the assets and data that are needed for efficient rescue and repurposing, innovative ideas for new uses of these resources come from a variety of organizations, including NIH. In April 2011, NIH convened a meeting of leaders from industry, government, academia, and the non-profit sector to explore the challenges and opportunities of drug rescue and repurposing. The *NIH-Industry Roundtable: Exploring New Uses for Abandoned and Approved Therapeutics* included an overview the landscape, an analysis of the use of collaborative efforts, and the identification of the key components of a framework for future collaborative agreements. At the conclusion of the meeting, the participants agreed to continue working together to further develop the policy and programmatic steps that need to be taken to foster drug rescue and repurposing projects.

Discussions among the participants are continuing through a cross-sector working group, which focuses on identifying potential drug rescue pilot projects for NIH-industry collaborations and refining core principles and draft terms for a framework for future collaborative agreements, including technology transfer. It will also engage academic investigators and explore ways to facilitate the identification and realization of promising opportunities for collaborative projects between industry and academia.

NIH is also developing a comprehensive database of approved and investigational drugs (the National Chemical Genomics Center Pharmaceutical Collection) and working to incorporate rescue and repurposing efforts into the portfolio of the National Center for Advancing Translational Sciences, fund pilot projects, and further engage with the Food and Drug Administration to advance opportunities in this promising area.

Item

Dystonia Coalition. - The Committee commends ORDR for the work conducted in the Rare Diseases Clinical Research Network and requests an update on the patient registry of the Dystonia Coalition. (p. 108)

Action taken or to be taken

The Rare Diseases Clinical Research Network (RDCRN) Patient Contact Registry enables investigators to reach patients with rare diseases who are interested in participating in clinical research studies. Interested patients are able to register their names and contact information with

the Registry. In addition to facilitating access to information about clinical trials, the Registry is also a source of information for patients about the progress of research projects in which they participate.

The Dystonia Coalition Patient Registry was made available to the public December 1, 2011. Within one month, 1,271 individuals had registered. Patient Advocacy Groups are also actively advertising the availability of the registry. The Coalition consulted with NIH in developing the Registry and has incorporated the Common Data Elements (CDEs) developed for the Office of Rare Diseases (ORDR) Global Rare Diseases Patient Registry and Data Repository (GRDR). Using the CDEs will facilitate the harmonization, sharing, and exchange of information across registries. Information about the Dystonia Coalition Patient Registry was disseminated at the 5th International Dystonia Symposium in Barcelona, Spain, October 20-22, 2011, and introduced to European patient advocacy groups in attendance.

Item

Hereditary Angioedema [HAE]. - The Committee encourages ORDR and relevant Institutes and Centers to expand research on HAE, a rare and potentially life-threatening genetic condition. In particular, the Committee urges ORDR to support a scientific conference on HAE, with the goal of identifying research opportunities and priorities for this disease. (p. 108)

Action taken or to be taken

Hereditary Angioedema (HAE) is a rare genetic disorder where patients suffer from attacks of severe swelling of the hands, feet, abdomen, face and /or throat. Swelling of the throat is a particularly serious and, sometimes, life-threatening manifestation that can require emergency medical treatment. Estimates for the prevalence of HAE range from one in 10,000 to one in 50,000 people in the United States.

NIH supports basic and clinical research to advance understanding of the disease and develop approaches to treat its symptoms and provides support for the training of investigators focused on HAE. For example, the Mount Sinai Clinical and Translational Science Award provided infrastructure support, consisting of core laboratory resources, patient recruitment and monitoring facilities, and regulatory knowledge support, for the *Phase III Randomized Double Blind, Placebo controlled Multicenter Study of Icatibant for Subcutaneous Injection in Patients with Acute Attacks of Hereditary Angioedema*. This led to the August 2011 approval by the U.S. Food and Drug Administration (FDA) of icatibant subcutaneous injection (*Firazyr*, Shire Human Genetic Therapies, Inc.) for the treatment of acute attacks of hereditary angioedema in adults aged 18 years and older. This approval is an important advance for HAE because *Firazyr* can be self-administered by patients upon onset of an HAE attack. To stimulate research activities and applications on HAE, NIH encourages investigators and advocates of HAE research to apply for scientific conference grants to help identify further research opportunities and needs, and to develop an agenda and priorities for HAE research. The Office of Rare Diseases Research (ORDR), collaborating with other NIH research institutes, provides advice to interested organizations and investigators on how to apply for conference support.

We would also encourage advocacy groups for HAE to apply for an ORDR pilot project, the Global Rare Diseases Patient Registry and Data Repository (GRDR). The goal of the GRDR is to enable analyses of data across many rare diseases and to facilitate clinical trials and other studies. During the pilot project, 12 patient groups that do not yet have patient registries will be selected to assist in testing the GRDR web based template designed to help establish patient registries and to measure the effectiveness of Common Data Elements (CDEs) that would facilitate the harmonization, sharing, and exchange of information across registries and diseases. Twelve additional existing patient registries will also be selected to integrate their data into the GRDR. A request for information from interested patient support organizations will be released and widely circulated in the near future and will inform organizations focusing on rare diseases, including HAE, of the opportunity to participate in the pilot project. Based on earlier NIH- supported studies, two agents were approved by the FDA in 2009 for the treatment of HAE: a plasma-derived C1-esterase inhibitor concentrate for injection (*Berinert*, CSL Behring, Inc) for the treatment of adults and adolescents with HAE-related acute abdominal attacks and facial swelling, and ecallantide subcutaneous injection (*Kalbitor*, Dyax Corp) for the treatment of sudden and potentially fatal fluid build-up associated with HAE in patients aged 16 years and older.

Conference Significant Items

Item

Accelerating Commercialization of Therapies to Patients. - The conferees understand the need to develop models to assist research universities and institutes on the best ways to leverage and commercialize federally supported basic and applied biomedical research discoveries. This is a key reason why the conferees have agreed to create NCATS. The conferees note the market has started to develop public-private sector models that are beginning to show results in translating basic research far more quickly than traditional models. These types of models use pre-defined technology-licensing terms to rapidly license new products and build a core of options for commercialization partnerships with pharmaceutical and biotechnology companies to establish joint ventures to further advance products to the market. The conferees strongly urge NIH to study and foster these models. The conferees expect any NIH-supported partnerships to expand translational pharmaceutical development in a manner that does not inhibit creative market models. Top priorities of the Center should include developing tools to improve the "de-risking" process and advancing the drug development process to the point at which it can reasonably be expected to be picked up by the private sector. The conferees suggest the selection of Center projects should consider future market acceptance as one component of the criteria to evaluate and select potential Center projects. The conferees direct NIH to host a trans-NIH workshop with key research organizations, venture capitalists, pharmaceutical firms, the PTO, the FDA, and a sample of research universities and institutes to work together with NIH and the drug development market. The workshop should also consider how existing NIH and government mechanisms can be used to encourage models around the country to speed commercialization of therapies through a market-based approach. (p. 35)

Action taken or to be taken

In a move to re-engineer the process of translating scientific discoveries into new drugs, diagnostics, and devices, Congress established the National Center for Advancing Translational Sciences (NCATS). The new Center will catalyze innovations in translational science and, in collaboration with partners in the regulatory, academic, nonprofit, and private sectors, work to identify and overcome hurdles that slow the development of effective treatments and cures.

There is growing recognition of the value of research collaborations to engage the strengths and expertise of multiple sectors in translating new discoveries into clinically useful products. NCATS will address critical gaps in the therapeutics development pipeline and help overcome roadblocks to private sector commercialization of federally-funded research and development. Building multi-sector collaborations to leverage cross-sector research expertise and expand the scope of the precompetitive drug development pipeline is a key strategy.

NCATS will be continuing efforts begun in 2011 to build collaborations with key stakeholders from the pharmaceutical and biotechnology industry, academic institutions, and non-profits. In April 2011, a joint NIH-industry workshop on drug rescue and repurposing explored partnerships to develop new uses for abandoned and existing drugs. Current follow-on activities are laying the foundation for collaborations with industry to provide academic investigators with access to candidate drugs that can be further developed and commercialized. NIH also sponsored a workshop in November 2011 with industry and academic experts to explore collaborative strategies to better validate drug targets emerging from basic biomedical research. The two day meeting culminated in an agreement among participants to establish cross-sector, precompetitive collaborations to advance target validation research and systems development. Follow up activities are focused on developing high priority pilot projects and tools and resources to support target validation studies.

To explore other critical translational areas and innovative public-private sector partnership models, NCATS will be working with other NIH Institutes and Centers to convene additional workshops with industry, venture capital, other research funders, and non-profits as well as the Food and Drug Administration, and the Patent and Trademark Office. For example, in FY 2012, NCATS will bring these stakeholders together to explore models to advance medical device innovation and models for commercializing research on new indications for compounds at or near the end of their patent life.

Item

Clinical and Translational Science Awards [CTSAs]. - The conferees are encouraged by the success of the CTSA consortium and recommend the program receive full funding as it nears full implementation. The conferees expect the NCATS Director to ensure the current focus on the full spectrum of translational research is maintained, and CTSA resources are not diverted. The inclusion of patient-centered research, community engagement, training, dissemination science, and behavioral research is extremely important to the translation and application of basic science discoveries and success of the CTSAs. CTSAs now represent an investment of half a decade of innovation in translational research. To ensure the benefits of this investment are maintained, the conferees urge NIH to support a study by the IOM that would evaluate the CTSA program and

recommend whether changes to the current mission are needed. The review should include stakeholders' input and be available no later than 18 months after the enactment of this bill. (p. 36)

Action taken or to be taken

CTSAs have broad experience and expertise along the full spectrum of translational research. NCATS plans to ensure that the benefits of the CTSA Program are maintained and, indeed further strengthened, by careful and rigorous external evaluation of all aspects of this major investment, including assessment of the overall mission and examination of all aspects of scientific oversight and productivity. In 2010, the NIH initiated the CTSA National Evaluation, a rigorous external review that includes 1) a field visit component--to obtain an in-depth picture of how the CTSA network is being implemented, 2) surveys of user communities, 3) bibliometric analyses, and 4) a study of potential scientific breakthroughs. Final reports from this evaluation will be available in winter 2012. In addition, in December 2011 NIH received the final report from an investigation from the Office of the Inspector General of the NIH administration of the Clinical and Translational Science Awards Program. This report identified a number of areas that must be strengthened in the management of these grants. In light of these reports, NCATS does not feel that an additional, potentially duplicative, report by IOM is necessary at this time. The new NCATS leadership will consider carefully both external assessments and will take appropriate steps to increase the impact of the CTSA consortium.

Office of the Director (OD)

Senate Significant Items

Item

Angiogenesis. - The Committee encourages NIH to support research that will determine the role angiogenesis may have in disease prevention and intervention. The Trans-Institute Angiogenesis Research Program should implement a vigorous agenda that examines current angiogenesis therapies in order to improve outcomes. In particular, the Committee urges NCI to take a leading role in examining angiogenic levels in the body prior, during and after treatments. The Committee urges NIH to use current population studies to determine the angiogenic effect of medication, diet and lifestyle. In addition, all relevant institutes are urged to coordinate efforts to study the correlation of platelet proteomes to angiogenesis with the goal of developing a health marker. (p. 109)

Action taken or to be taken

NCI funds angiogenesis-related research that includes examination of the angiogenesis of cancer cells and exploration of therapies targeting this process, as well as research on diet, angiogenesis, and cancer prevention. NCI is planning to host a scientific workshop in 2012 to bring together experts in angiogenesis and nutrition to explore current science regarding angiogenesis modification, diet, and cancer. Research is also underway to investigate the effect of moderate intensity exercise on blood vessels of cancer biomarkers related to angiogenesis.

NCI-supported research has shown that the inhibition of certain pathways may result in synergistic anti-tumor activity. For example, results of an NCI Phase 1 study evaluating the combination of the targeted therapies vandetanib and bevacizumab in patients with advanced solid tumors and lymphomas showed that the combination of agents caused dual blockades of one of the pathways, and provided preliminary evidence of both clinical improvement and anti-angiogenic effect. Other ongoing clinical trials are examining other combinations of anti-angiogenic drugs and radiation therapy for prostate and central nervous system cancers.

Several advances in understanding the mechanisms of angiogenesis have been reported this year, and these findings may lead to improvements in treatment, overcoming drug resistance, or more effective drug delivery for cancer patients. NCI investigators have discovered a pathway to control signaling that may overcome side effects of Avastin therapy, such as hypertension and thrombosis. This discovery may lead to improvements in survival and quality of life for patients receiving Avastin. NCI researchers have also discovered that TIMP-2, a protein observed in unusually low levels in cancer patients, functions to suppress tumor growth by inhibiting angiogenesis. Since the protein is normally present in the human body, it may have fewer toxic effects than traditional chemotherapy drugs. In another recent study, NCI researchers discovered that a receptor called **GPR124** functions as an important regulator of neurovasculature development, which may lead to new therapeutic approaches in the treatment of cerebrovascular diseases.

NCI-supported researchers examining mechanisms of resistance to certain targeted drugs for glioblastoma multiforme (a type of brain cancer), colorectal carcinoma, and hepatocellular

carcinoma have found a significant correlation between high circulating levels of a particular pro-angiogenic protein and its receptor, suggesting that they may be key factors in the development of drug resistance. Studies of plerixafor, an approved therapy to block the receptor, have shown that treatment with plerixafor can prolong survival in glioblastoma multiforme and colorectal cancer patients. NCI is also testing several experimental anti-angiogenesis therapies in patients with Kaposi's Sarcoma.

Other related angiogenesis research includes examination of the collagen barriers produced by some tumor host cells (stroma) by pancreatic and other cancer types and the resulting problems for delivery and efficacy of anti-cancer drugs. Using preclinical models, researchers have found that losartan, an FDA approved drug for treating hypertension, can "open" compressed tumor vessels and make the dense pancreatic cancer stroma more permeable. Because losartan is a safe and widely used anti-hypertensive drug, these findings offer a rapidly translatable strategy that may improve the treatment of pancreatic cancer in humans. Efforts are underway to test whether adding losartan to standard therapy can improve survival.

Item

Autism. - The Committee encourages NIMH, NINDS and NICHD to expand their support for the development of clinically based therapeutics for autistic children through the use of a variety of mechanisms, including grants, contracts and the Small Business Innovation in Research program. (p. 109)

Action taken or to be taken

The National Institute of Mental Health (NIMH), National Institute of Neurological Disorders and Stroke (NINDS), and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) are committed to furthering research to develop clinically based treatments for people with autism spectrum disorder (ASD), including biomedical and behavioral interventions. These institutes support several funding opportunities that solicit applications to support research on ASD therapeutics: Research on Autism and ASD; NIH Autism Centers of Excellence (ACE) Centers Networks; Psychosocial/Behavioral Interventions and Services Research in ASD. Projects across the ACE program are investigating the effectiveness and safety of specific therapeutics on symptoms and behaviors associated with ASD. The University of California, Los Angeles ACE is examining the effects of risperidone on repetitive behaviors and brain activity in children and adolescents with ASD. The University of Illinois, Chicago ACE is conducting a clinical trial of escitalopram for treating rigidity in children and adolescents with ASD. The Wayne State University ACE is conducting a multi-site trial to test the safety and efficacy of buspirone as an early intervention in children with ASD under the age of 6 years.

In addition to the ACE program, NICHD is funding a multi-site trial to provide evidence-based guidance in the selection and monitoring of medications for children with ASD. This is the first comparative effectiveness trial of the effects of aripiprazole and risperidone on social engagement, mood, and language. Following the discovery of abnormal sleep patterns in children with ASD, NIMH's intramural research program (IRP) recently demonstrated that donepezil may normalize the sleep in young children with ASD. The IRP has had an important

role in pilot testing novel compounds as potential treatments for ASD-related impairments, and has already evaluated over 500 children.

In addition to new medications, NIH continues to support research to improve delivery of evidence-based behavioral interventions for people with ASD. Studies have shown the importance of early intervention. For example, an NIMH-funded study found that children with ASD who receive a high intensity behavioral intervention starting by age 18-30 months show improvements in IQ, language, adaptive behavior, and severity of diagnosis. To better identify ASD and deliver early interventions, the NIMH Small Business Innovation Research (SBIR) program has funded three separate projects to: develop a web-based program that parents can use with young children with ASD to promote core social skills; create a web-based program to train psychology graduate students to screen for ASD in children ages 3-10; and, design a web-based computerized questionnaire for parents of children ages 18 months to 3 years, to complete prior to pediatric appointments. Additionally, an NINDS SBIR project is developing a software system and web-based toolset to improve pediatricians' accuracy and speed in identifying ASD in children age 3 and younger.

Current NIMH-funded studies are working to make screening, treatments, and services for people with ASD available across diverse populations and settings. One set of studies aims to reduce the age of screening and diagnosis for children from both Latino and African American families, as well as examine the effectiveness of telehealth-delivered ASD treatment in rural settings. Together, NIH's biomedical and behavioral research is advancing us towards the next generation of clinical therapeutics for improving the lives of people with ASD and their families.

Item

Black Scientists. - The Committee is deeply disturbed by the recent study which found that between 2000 and 2006, black scientists were much less likely to win approval of RO1 grants than white scientists, even after controlling for the education level of the applicants and the academic institution where they work. Also of concern is the disproportionately low number of black researchers who applied for a grant - just 1.5 percent of all applicants. In addition, the study raises questions about the effectiveness of NIH's graduate and postgraduate training, as black researchers do not seem to benefit from this training as much as white researchers do. The Committee notes that NIH itself funded this study and that the agency appears to be responding with significant actions designed to redress the disparities. Ultimately, however, NIH will be judged on whether the disparities are reduced. The Committee requests an update on this issue in the fiscal year 2013 congressional budget justification. (p. 109-110)

Action taken or to be taken

NIH commissioned a study, published in *Science* on August 19, 2011, to examine the relationship of an applicant's race and ethnicity to the level of success on NIH R01 grant applications. The paper by Ginther, *et al.* found that Black scientists were 10 percentage points less likely to receive funding even after controlling for other observable factors. The same issue of *Science* included a Policy Forum by the NIH Director and Deputy Director outlining steps NIH is taking to address the the observed differences in review outcomes, as well as low participation rates for certain racial and ethnic groups.

NIH shares the Committee's concerns and is indeed working to redress the disparities. Of note, the agency's efforts in this regard are significantly affected by three interrelated challenges: (1) the need to better engage racial and ethnic minority students in science during the K-12 educational period, .

(2) severe underrepresentation of racial and ethnic minority degree-holders in science and engineering at both the Baccalaureate and PhD level , and (3) underrepresentation of racial and ethnic minorities among the applicant pool for NIH grants.

To address the critical issues related to R01 success rates, NIH is taking the following steps:

- Expanding a recently developed Early Career Reviewer Program. NIH learned through the Ginther, *et al* study that an applicant's prior experience on peer review panels is one factor that may reduce the gap observed for Black scientists. Therefore, this program will encourage promising junior faculty and others who previously have not received NIH funding to participate in peer review panels, so they can learn how review groups evaluate and score grant applications and can apply this knowledge to strengthen their own grant applications. NIH is making a special effort to inform investigators from underrepresented groups about this program. The agency recently requested nominations of faculty members and researchers from a broad range of institutions, including Historically Black Colleges and Universities, who are actively involved and established in biomedical research and have published in high-quality scientific journals, but who may not yet have received major peer-reviewed research support. NIH is also allowing faculty to self-nominate for the program.
- Carrying out studies to further understand the observed differences in peer review outcomes. This includes examining the effects of the racial and ethnic composition of peer review committee; the effects of intensive pre-application mentoring; and the effects of implicit bias training for peer reviewers.
- Investigating the impact of mentoring activities associated with the Ruth L. Kirschstein National Research Service Awards and the NIH Career Development Programs on racial and ethnic differences in peer review outcomes.
- Promoting and conducting research programs to identify and test interventions to improve diversity in the biomedical sciences such as the NIH Director's Pathfinder Awards.
- Examining and adapting recruitment efforts in the intramural research program to improve NIH's ability to recruit a diverse intramural scientific workforce.
- Conducting an analysis and continuous evaluation of the outcomes of diversity-targeted research training and career development programs in an effort to inform future enhancements of the agency-wide approach to diversity.
- Identifying further ways to increase diversity within the intramural and extramural programs through the work of the NIH Steering Committee's Diversity Working Group, which was established in 2010.
- Identifying innovative solutions to barriers in career advancement for scientists from underrepresented groups by constituting a new working group of the NIH Director's Advisory Committee. This committee is co-chaired by Dr. Reed Tuckson, Executive Vice President and Chief of Medical Affairs, UnitedHealth Group, the NIH Principal Deputy Director, and the Director of NIMHD.

Item

Bone Research. - The Committee urges the Director to work with all relevant institutes to enhance interdisciplinary research leading to targeted therapies for improving bone density, quality and strength for all Americans. More scientific knowledge is needed in a number of key areas involving bone and muscle, fat and the central nervous system. Research is also urgently needed to improve the identification of populations who might require earlier treatment because they are at risk of rapid bone loss due to a wide range of conditions or diseases, including obesity, diabetes, chronic renal failure, cancer, HIV, conditions that affect absorption of nutrients or medications, or addiction to tobacco, alcohol or other opiates. The Committee also encourages NIH to develop a plan to expand genetics and other research on rare bone diseases, including: osteogenesis imperfecta, Paget's disease of bone, fibrous dysplasia, osteopetrosis, fibrous ossificans progressiva, melorheostosis, X-linked hypophosphatemic rickets, multiple hereditary exostoses and multiple osteochondroma. (p. 110)

Action taken or to be taken

NIH has supported several long-term epidemiologic efforts focused on fracture risk in older women and men to identify people who are at risk of rapid bone loss, and therefore may benefit from earlier treatment. For example, data from about 17,000 research participants in various NIH-funded studies revealed that two common measurement tools are able to, but underestimate, fracture risk in older adults who have type 2 diabetes. This finding suggests that modifying these effective and widely used tools would provide more accurate assessments and better care to patients with type 2 diabetes. Similarly, the Study of Osteoporosis in Men (Mr. OS) documented that bone mineral density (BMD) measurements also underestimated fracture risk in obese men, regardless of whether they had diabetes. The obese men in Mr. OS had diminished mobility and physical function, suggesting multiple behavioral strategies could prevent fractures. Other studies are investigating whether intensive treatment with insulin leads to a reduction of bone loss in people with type 1 diabetes, while another effort aims to assess the impact of interventions on bone loss in type 2 diabetes.

Although most fragility fractures occur in older adults, younger women can also be at risk. NIH-funded investigators are searching for methods to identify premenopausal women with very low BMD, who are at greatest risk for fracture. This ability would have considerable cost savings as well as a profound effect on patients' lives. Identifying easily measurable bone biomarkers could also lead to new therapeutic targets.

NIH-funded research on parathyroid hormone (PTH)—a key hormone responsible for regulating the cells involved in bone formation—led to its development as a treatment for osteoporosis. A current NIH-supported study is developing a long-acting form of the bone-building PTH. Other therapies for osteoporosis aim to inhibit the bone resorption process using a class of drugs called bisphosphonates (e.g., alendronate). Counter intuitively, clinical trials using both drugs at the same time showed that alendronate impaired, rather than complemented, the effects of PTH. NIH-funded researchers recently uncovered a biochemical explanation of this clinical phenomenon, suggesting that use of PTH before antiresorptive therapy could be more effective than the reverse sequence or simultaneous administration. Moreover, the elucidation of the mechanisms underlying bone turnover may also help to provide a basis for future therapies.

NIH-funded researchers are also investigating interactions between bone and other organ systems. One recent study demonstrated that developing bones secrete molecules that may affect muscle development. Another important advance involving the bone's communication with the kidneys has led NIH-supported scientists to a potential treatment for a form of rickets called X-linked hypophosphatemia (XLH). In addition, researchers have found that vascular endothelial cells, which line the walls of blood vessels, are a main source of the excess bone that develops in people who have fibrodysplasia ossificans progressiva (FOP).

The NIH-sponsored International Meeting on Fibrous Dysplasia of Bone/McCune-Albright Syndrome in October 2010 brought together experts for the purpose of building collaborations, identifying scientific opportunities, and defining best clinical practices. Meanwhile, the Federal Working Group on Bone Diseases—an interagency committee led by NIH—offers a forum for sharing information and facilitating collaborative bone research activities based on each agency's mission. NIH contributors include NIAMS, NCI, NIA, NIAAA, NIBIB, NICHD, NIDCR, NIDDK, NIEHS, NINR, NCCAM, NCATS, ORS, ORDR, and ORWH.

Item

Chemical Risk Assessment. - The Committee understands that NIH supports a new approach on chemical risk assessment based on the incorporation of advanced molecular biological and computational methods in lieu of animal toxicity tests as outlined in a recent National Research Council report. As part of that effort, the Committee encourages NIH to continue to support extramural and "proof of concept" studies on the use of toxicity pathway analyses for assessing human risks to chemical exposures. The Committee requests an update on these efforts in the fiscal year 2013 congressional budget justification. (p. 110)

Action taken or to be taken

The U.S. Tox21 program is a collaboration of four government organizations – the National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP), the NIH Chemical Genomics Center (NCGC), the Environmental Protection Agency, and the Food and Drug Administration – to shift toxicology from classical animal studies to target-specific, mechanism-based, biological observations largely obtained using *in vitro* assays. The goals of Tox21 are to (1) research, develop, validate, and translate innovative testing methods that characterize toxicity/disease pathways; (2) identify mechanisms of compound-induced biological activity in order to characterize toxicity/disease pathways, facilitate cross-species extrapolation, and provide input to models for low-dose extrapolation; and (3) develop predictive models for adverse health effects in humans. This approach, based on understanding cellular pathways linked to disease, is equally valid for identifying hazardous chemicals and potential new drugs.

Tox21 Phase IIa was initiated in FY 2012 and will continue into FY 2013. In this phase, a 10,000 (10K)-compound library is being screened in biochemical- and cell-based quantitative high-throughput screens using an NIEHS-funded robotics platform at NCGC. The focus is on nuclear receptor assays to detect endocrine active compounds and stress response assays to detect highly reactive compounds. The library includes many types of chemicals, from those with almost none to extensive toxicological information as well as those with use, production, and/or environmental exposure patterns that make them of potential concern to regulatory agencies.

About 30 percent of the compounds are marketed drugs, which will allow Tox21 data to be linked to human response information. Chemical analysis to determine the identity, purity, concentration, and stability of each of the approximately 10K compounds continues into FY2013. Informatic tools for data analysis to permit prioritizing chemicals for more extensive testing and prediction models continue to be developed as more data become available. In ToxCast, EPA's contribution to Tox21, screening was completed for a 700-compound subset of the 10K library across more than 500 in vitro assays, as well as assays using lower organisms (e.g., zebrafish embryos, the roundworm *Caenorhabditis elegans*); data analysis will continue through FY 2013. All data generated in Tox21 are being made publicly available in several databases, including NTP's "Chemical Effects in Biological Systems."

In FY 2013, screening efforts at NCGC will focus on using human cell models coupled with high-throughput genomic arrays to evaluate the effects of chemicals on multiple cellular pathways that involved in human disease. During FY 2012 and FY 2013, NIEHS continues to support the development of technologies, assays, and computational methods useful for Tox21 in the areas of epigenetics, human variability in response, engineered tissue models, and disease pathway identification (e.g., autism, diabetes, obesity). In support of this effort, NIEHS is making available to the scientific community a 1,000-compound library of toxicants, a database allowing investigator data to be linked to classical toxicology, human toxicity, and Tox21 data and provides informatics tools for mining these data.

Item

Chimpanzees. - The Committee is eagerly anticipating the release later this year of the Institute of Medicine's analysis of whether chimpanzees should continue to be used in medical research. (p. 110)

Action taken or to be taken

In April 2011, NIH commissioned the Institute of Medicine (IOM) to conduct a study to assess the current scientific need for the continued use of chimpanzees to accelerate biomedical discoveries and biomedical research. The IOM's 12-member expert study panel has met several times, including a public workshop in August where noted experts in biomedical and behavioral research as well as members of the public provided input on the issues. More information on the study is available on the IOM's website (<http://iom.edu/Activities/Research/Chimpanzees.aspx>).

On December 15, the IOM issued its findings, with a primary recommendation that the use of chimpanzees in research be guided by a set of principles and criteria. The IOM committee concluded that "while the chimpanzee has been a valuable animal model in past research, most current use of chimpanzees for biomedical research is unnecessary." The committee also concluded, however, that the following areas may continue to require the use of chimpanzees: some ongoing research on monoclonal antibody therapies; research on comparative genomics; and noninvasive studies of social and behavioral factors that affect the development, prevention, or treatment of disease. The committee was unable to reach consensus on the necessity of the chimpanzee for the development of prophylactic hepatitis C virus vaccine. While the committee encouraged NIH to continue development of nonchimpanzee models and technologies, it

acknowledged that new, emerging, or re-emerging diseases may present challenges that may require the use of chimpanzees.

After careful consideration, NIH accepted the recommendations and is developing a plan to implement the IOM's guiding principles and criteria. A working group of the NIH Council of Councils will be assembled to advise on the implementation of the recommendations and to consider the size and placement of the active and inactive populations of NIH-owned or -supported chimpanzees. NIH will not issue any new awards for research involving chimpanzees until processes for implementing the recommendations are in place (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-025.html>).

Item

Chronic Fatigue Syndrome [CFS]. - The Committee commends NIH for holding a state of the knowledge workshop on CFS in 2011. Within 1 year following that workshop, the Committee urges NIH to develop a CFS research plan outlining a coordinated strategy for intramural and extramural research on CFS and related funding opportunity announcements. Further, the Committee supports the development of a CFS research database to catalogue the intramural and extramural NIH research funding that has been awarded for CFS research to date and the resulting advances. (p. 110)

Action taken or to be taken

The 2011 State of Knowledge Workshop on Chronic Fatigue Syndrome (CFS) [sometimes referred to as myalgic encephalomyelitis (ME)] brought together 32 experts from many scientific fields to discuss the gaps in our knowledge of ME/CFS and opportunities for advancing research on this debilitating illness. A copy of the workshop report can be found on the Trans-NIH ME/CFS Research Working Group website (<http://orwh.od.nih.gov/CSF%202011/SoK%20Workshop%20Report%20508%20compliant%20-%208-5-11.pdf>). Presentations and discussions at the workshop supported the need for NIH to reissue a funding opportunity announcement to solicit research applications on ME/CFS over the next three years that focuses on etiology, prevention, diagnosis, pathophysiology, and treatment. Two funding opportunities; PAR-12-032 and PAR-13-033 for ME/CFS were published in the NIH Guide for Grants and Contracts on November 18, 2011.

The Working Group, coordinated by Office of Research on Women's Health (ORWH), meets on a regular basis to enhance awareness of ME/CFS and to consider ways to improve the integration of ME/CFS into other NIH extramural and intramural research initiatives (e.g., chronic pain, retrovirology, brain disorders, immunology, and genetics).

NIH has an existing database that is ideally suited to catalogue NIH research funding for ME/CFS. Referred to as RePORTER (<http://projectreporter.nih.gov/reporter.cfm>), the database is publicly accessible and user friendly, links to research projects funded by NIH, provides details on the principal investigator, and lists publications resulting from that award. ME/CFS projects and total funding are also identified on the NIH Estimates of Funding for Various Research, Condition, and Disease Categories webpage (<http://report.nih.gov/rcdc/categories/>).

Item

Class B Animal Dealers. - The Committee is encouraged by the steps NIH is taking to increase the capacity of Class A vendors to supply the types of dogs that currently come from Class B random source dealers; to notify its grant recipients that as of 2015, the use of NIH grant funds to acquire dogs from Class B dealers will be prohibited; and to advise its grantees to identify new sources for such animals. The Committee urges NIH to set 2015 as the outside target date for completing this process. Meanwhile, NIH has informed the Committee that no phase out of cats from Class B vendors is needed, because sufficient numbers of cats currently are available through Class A vendors to support the needs of NIH-supported research. If there is already no need for Class B cats in NIH-funded research, the Committee sees no reason why NIH should wait until Class B dogs are prohibited a process that will take at least 3 years to prohibit the use of Class B cats as well. The Committee therefore expects NIH to begin informing researchers of this policy as soon as possible and requests an update in the fiscal year 2013 congressional budget justification. (p. 110-111)

Action taken or to be taken

Class A Dogs

NIH has developed and implemented a pilot program that supports establishment of a Class A vendor resource with a breeding capacity to provide sufficient numbers of mature, large, socialized, out-bred hounds or mongrel research dogs to be used in place of dogs now acquired through Class B dealers. Because new breeding colonies must be established and time is needed to breed, whelp, wean, socialize, and raise animals to a size and age appropriate for research, the phase-in period is anticipated to last for several years. In transitioning from Class B to Class A purpose-bred dogs, it is critical to validate the suitability of the animals provided through this contract for scientific research, to ensure that important research studies are not jeopardized. The acquisition began in FY 2011 and involved a small number of animals that were used to evaluate scientific suitability. With annual increases, it is expected that a majority of the dogs used for research will be available from this vendor resource by FY 2014. The contract is being closely monitored while the number of animals provided to investigators increases. More information regarding the scientific suitability of purpose-bred dogs will become available. It is expected that this scaled-up resource as well as additional private sector sources will enable full phase-in of the new NIH Class A dog policy by 2015.

On March 18, 2011 NIH issued a policy statement for the research community (NOT-OD-11-055 <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-11-055.html>) informing them of the transition and eventual phase out of the use of research animals provided by Class B vendors and encouraging researchers to begin planning for this transition as soon as possible. Subsequent to the full transition and evaluation, the use of NIH research funds to purchase dogs from Class B dealers will no longer be allowed and a new policy announcement to that effect will be issued. NIH will provide training to extramural staff about the implementation of the new policy and will provide information to the research community about how to access Class A dogs.

Class A Cats

NIH agrees that from a supply standpoint alone, it may be possible to implement a requirement for the use of Class A and other private sector sources of cats (e.g., intra-institutionally purpose-bred or donated animals) without a phase-out period for the use of Class B cats. NIH will publish a Notice in the NIH Guide for Grants and Contracts to inform the research community about the planned change in policy restricting the sources of cats used in NIH-funded research. NIH intends to move ahead with the implementation of the policy.

Item

Cystic Fibrosis [CF]. - While the life expectancy of CF patients has slowly improved, the Committee remains concerned regarding the severe morbidity and early mortality associated with the condition and acknowledges that improvements to date have largely focused on enhanced supportive care. The Committee cites the strong need for further research regarding treatments that target the underlying cause of CF and recognizes that protein structural studies may advance the understanding of the mechanisms of action of CF drugs in clinical development. The Committee encourages support for such protein structural studies and encourages the use of new technologies to discover, develop and characterize the effect of new treatments, including the use of airway imaging to characterize the function of the airways. The Committee also notes the potential for research in CF to have applications on a wide array of human diseases, and urges continued work to identify the applications of CF treatments to other disease states. (p. 111)

Action taken or to be taken

Identifying therapies to reduce the burden of illness and expand life expectancy in CF patients remains an important NHLBI priority. The Institute continues to support a vigorous basic and clinical research program that promotes a better understanding of the underlying pathophysiology of CF and supports investigations of new treatment options. Key questions regarding pathogenetic mechanisms in CF are being answered, ongoing clinical trials are contributing to the steady improvement in the clinical management of CF, and the recent development of large-animal models and newer murine models of this disease provide fresh opportunities for research and therapeutic development. Current treatment advances in CF have been largely directed at established disease in older children and adults, but newborn screening provides an opportunity to preempt and prevent CF lung disease earlier. NHLBI recently released an initiative to explore the mechanisms involved in development, progression, and severity of lung disease in infants and young children with CF; it includes development of innovative biomarker and imaging approaches to assess structural changes and physiologic function.

An emerging field in CF therapy is the development of treatment strategies that address the basic defect in structure and function of the CF transmembrane conductance regulator protein (CFTR), rather than just alleviate the symptoms. Small-molecule “corrector” and “potentiator” drugs that partially reverse the CF genetic defect or improve protein function have shown promise in early-stage clinical trials. Because these novel classes of drug treatments currently target only a small subset of CF patients, NHLBI recognizes the need for additional research to explore their utility in patients with other mutations and in combination with other therapies to identify the optimal

drug classes/drugs for each CF patient. Further structural and functional studies of CFTR are important for the continued development of these new therapies and will be an area of focus in an upcoming 2012 NHLBI workshop, Protein Structure and Lung Disease.

CF-related diabetes (CFRD) is one of the most common complications of CF, occurring in almost half the patients as they age and becoming more prevalent as the life expectancy of CF patients improves. CF patients with CFRD experience more illness and earlier death than those who do not develop CFRD. It is not currently known why some patients develop CFRD, although some genetic variants have been implicated. NIDDK recently issued a new initiative to encourage research to understand the causes and consequences of CFRD. NIDDK-funded research led to the recent development of a ferret CF model. Ferrets with CF exhibit pulmonary, digestive, and diabetic complications much more similar to those observed in humans with the disease than are seen in other animal models. The ferret model is expected to be highly valuable for the study of CF complications and potential treatments.

Item

Eosinophil-Associated Disorders. - The Committee urges NIH to prioritize research on eosinophilic disorders and develop a trans-institute strategy involving NIAID, NIDDK, NICHD and NIMH. Multidisciplinary research efforts are needed to develop improved methods of diagnosis and treatment in adults and children and to assess strategies for managing depression and emotional stress in patients with severe eosinophilic disorders. NIH should seek opportunities to collaborate with private sector organizations on this initiative. The Committee requests an update on this effort in the fiscal year 2013 congressional budget justification. (p. 111)

Action taken or to be taken

NIH continues its trans-NIH approach to the support of research on eosinophilic disorders. A number of Institutes and Centers are working together to better understand, identify, prevent, and treat eosinophilic and eosinophil-associated disorders. These collaborations have led to joint initiatives, workshops, and other activities in support of eosinophilic disorders research. Beginning in FY 2011, NIAID is coordinating a working group (of academic investigators and NIH representatives from NIAID, NIDDK, NHLBI, and NCI) to identify research needs on eosinophilic disorders and to develop a white paper on research on eosinophilic disorders.

NIH collaborations, such as the Consortium of Food Allergy Research co-sponsored by NIAID and NIDDK, continue to support the development of novel approaches to prevent and treat food allergy, including investigations of the mechanisms of food allergy-associated eosinophilic esophagitis (EoE). The NIAID Exploratory Investigations in Food Allergy Program, funded in partnership with the Food Allergy Initiative and the Food Allergy and Anaphylaxis Network, supports a study on the effect of acidity on mast cells and eosinophils. In FY 2012, NIAID will re-compete the Asthma and Allergic Diseases Cooperative Research Centers initiative, which supports innovative basic and clinical research on the biological mechanisms, immunological basis, diagnosis, treatment, and prevention of asthma and allergic diseases, including studies on the pathogenesis of EoE. NIAID intramural researchers continue to study a cohort of over 250 patients with eosinophilic disorders ranging from benign eosinophilia to eosinophilic leukemia.

Ongoing studies investigate the role of eosinophils in these disorders with the aim of identifying biomarkers of disease and developing targeted therapies.

NIDDK supports a portfolio of basic, translational, and clinical research on the causes and treatment of eosinophilic gastrointestinal disorders (EGIDs) to enhance understanding of these disorders and to improve diagnosis and treatment. NIDDK continues its efforts to catalog clinical, pathologic, and translational outcomes for children with eosinophilic esophagitis, comparing the effectiveness of dietary modifications versus the use of steroid medications. NIDDK will continue to pursue the National Commission on Digestive Diseases' recommendations for research on EGIDs.

The NIH Office of Rare Diseases Research partners with NIAMS and NINDS to support the Vasculitis Clinical Research Consortium (VCRC), a part of the Rare Diseases Clinical Research Network. The consortium has three active studies that include patients with Churg-Strauss Syndrome, a form of vasculitis featuring eosinophilia: a longitudinal Protocol for Churg-Strauss Syndrome; the VCRC Genetic Repository One-Time DNA Study; and Reproductive Health in Men and Women with Vasculitis.

NIMH continues to foster innovative research to develop greater understanding of mental disorders, including those that may be co-morbid with other physical diseases and conditions such as eosinophilic disorders. Ongoing NIMH research aims to better understand how the immune system influences gene expression and function in brain circuits that regulate affect, cognition, and social behavior.

Item

Fragile X. - The Committee urges NIH, working with NICHD, the Fragile X Clinical Research Consortium and the private research sector, to fully implement the NIH Research Plan on Fragile X Syndrome and Associated Disorders. NIH is encouraged to support translational research that shows significant promise of safer and more effective treatments for the various Fragile X-associated disorders. The Committee requests an update in the fiscal year 2013 congressional budget justification regarding the status of federally funded registry initiatives and how they might be coordinated. (p. 111)

Action taken or to be taken

In 2008, NICHD convened working groups charged with developing comprehensive research goals and specific research objectives for fragile X syndrome and the associated disorders of fragile X-associated tremor/ataxia syndrome, and fragile X-associated primary ovarian insufficiency. These working groups were composed of scientific experts from the research and clinical communities, representatives of affected individuals and family members, other pertinent federal agencies, and other NIH Institutes and Centers that support related research on fragile X syndrome. As a result of these meetings, the NIH published the *NIH Research Plan on Fragile X Syndrome and Associated Disorders* in early 2009 that was designed to be used by NIH, other federal agencies, and the academic research community to facilitate coordinated research activities on the detection, diagnosis, treatment, and prevention of these disorders. In the coming year, NICHD, along with the trans-NIH Fragile X Research Coordinating Group and others,

plans to hold another meeting to revisit the goals of the Research Plan. The primary objectives of the meeting will be to (1) assess the progress and relevance of the Research Plan's aims and (2) determine where additional research gaps remain.

NIH continues to maintain a substantial and diverse portfolio of fragile X-related research, including translational research that may lead to treatments and potential therapeutics to improve the lives of individuals with fragile X-associated conditions and their families. Using funds from the American Recovery and Reinvestment Act, NICHD made awards to two of its Intellectual and Developmental Disabilities Research Centers (IDDRCs) to develop a pilot version of a shared contact registry of individuals with intellectual and developmental disabilities (IDD). The IDDRC investigators used fragile X syndrome as a model. The contact registry has the potential to serve as a valuable resource for investigators interested in clinical studies involving fragile X and as a model for registries for other forms of IDD. For example, one of the investigators presented this promising registry model at a major NICHD-sponsored meeting that was convened in December 2010 to discuss the research resources needed in the field of Down syndrome. NICHD has encouraged the investigators working on this project to communicate with other groups developing registries related to rare diseases, including the CDC and the NIH Office of Rare Diseases Research.

Item

Global Rare Diseases Patient Registry and Data Repository. - The Committee commends NIH for its plans to develop the Global Rare Diseases Patient Registry and Data Repository [GRDR]. The Committee understands that a pilot program of the GRDR will include the creation of an infrastructure for an Internet based platform to aggregate de-identified patient data from existing and newly established rare diseases registries and the development of a web-based template to allow any patient group to establish its own patient registry. The purpose of this pilot program is to develop a resource for patient support organizations and the scientific community, academic centers and industry in the United States and globally to mine the de-identified, aggregate data for various medical research studies, including clinical trials. The Committee encourages NIH to consider Duchenne muscular dystrophy and glomerular disease for inclusion in the pilot program. (p. 111-112)

Action taken or to be taken

The Office of Rare Diseases (ORDR), in collaboration with PatientCrossroads, Children's Hospital of Philadelphia, and Medscape, launched a pilot project to establish the Global Rare Diseases Patient Registry and Data Repository (GRDR). The goal of the GRDR is to enable analyses of data across many rare diseases and to facilitate clinical trials and other studies. During the pilot project, 12 patient groups that do not yet have patient registries will be selected to assist in testing the GRDR web-based template designed to help establish patient registries and to measure the effectiveness of Common Data Elements (CDEs) that would facilitate the harmonization, sharing, and exchange of information across registries and diseases. Twelve additional existing patient registries will also be selected to integrate their data into the GRDR. A request for information from interested patient support organizations will be released and widely circulated in the near future and will inform organizations focusing on rare diseases, including

Duchenne muscular dystrophy and glomerular disease, of the opportunity to participate in the pilot project.

To assist the rare disease community, the ORDR has developed an informed consent template for participating in a patient registry. This template can be modified according to the specific needs of each registry and will be available to those groups participating in the GRDR pilot project.

Item

Hereditary Hemorrhagic Telangiectasia [HHT]. - The Committee urges the Director to bring together representatives from NHLBI, NINDS, NIDDK, NIAMS, NICHD, NCI and ORDR to develop a coordinated strategy for advancing research on HHT, particularly regarding translational research and early detection and intervention. (p. 112)

Action taken or to be taken

Hereditary Hemorrhagic Telangiectasia (HHT), also known as Osler-Weber-Rendu Syndrome, is a complex and rare inherited bleeding disorder that affects the vascular system (blood vessels). People with HHT develop abnormal blood vessels (arteriovenous malformations or AVMs) that lack the capillaries usually present between each artery and vein. The AVMs tend to be fragile and can rupture and bleed. Smaller AVMs are called Telangiectasia and occur primarily in the nose, mouth, skin of the face and hands, as well as the lining of the stomach and intestines. Larger AVMs occur in the brain, lungs, liver and spine.

Given the cross-cutting nature of HHT research, the Office of Rare Diseases Research (ORDR) is planning to convene a small working group of NIH Institute and Center (IC) representatives and patient support organizations to determine methods in which NIH can develop a coordinated strategy for advancing translational research on and early detection and intervention strategies for HHT within the Rare Diseases Clinical Research Network (RDCRN).

The RDCRN receives support from NIH and is composed of 19 distinct consortia working in concert to improve the availability of rare disease information, treatment, clinical studies, and general awareness for both patients and the medical community. The RDCRN also aims to provide up-to-date information for patients and to assist in connecting patients with advocacy groups, expert physicians, and clinical research opportunities. The RDCRN includes the Brain Vascular Malformation Consortium – an integrated group of academic medical centers at 12 locations and patient support organizations – that conducts clinical research on different forms of brain vascular malformations and works to improve the care of patients suffering from these disorders.

Additionally, because HHT can affect multiple organs (e.g., lung, brain, gut, liver), research efforts to address HHT span a number of NIH (ICs). NHLBI support has generated findings on specific gene defects in patients with HHT and progress in development of animal models, genetic tools, and methodology relevant to HHT research. NHLBI currently supports several grants that are pursuing fundamental and translational research to expand the understanding of molecular mechanisms and signaling pathways involved in HHT. Basic studies are exploring novel endothelial signaling pathways critical for vascular development and cell-cell interaction

in the brain, further defining the activin receptor-like kinase 1 (ALK-1)-endoglin signaling pathway highly implicated in vascular disorders such as HHT, and developing and using novel animal models for HHT to elucidate the pathogenetic mechanisms underlying vascular malformations. In the area of translational research, the new animal models are also being used to pursue potential therapeutic targets to prevent or reverse vascular malformations. This work, as well as complementary research supported by other Institutes, continues to produce new findings that could have direct clinical relevance for HHT. In addition, NINDS is currently supporting a study entitled *Cerebral Hemorrhage Risk in Hereditary Hemorrhagic Telangiectasia*, a longitudinal study to look at genetic and imaging characteristics of people with and without brain arterial malformations to learn more about their risk factors. NIAMS continues to explore ways to collaborate with other NIH ICs and to fund meritorious scientific research in areas relevant to its portfolio. Specifically, basic scientific pursuits by NIAMS-supported investigators help to inform all areas of science, including the study of HHT.

Item

Human Tissue Supply. - The Committee remains committed to matching the increased needs of NIH-funded researchers, both intramural and extramural, who rely upon human tissues and organs to study human diseases, both normal and rare, and strive to translate research advances and discoveries into treatments and cures. Furthermore, the Committee recognizes that meeting the national demand of production of high-quality biospecimens in a timely manner is crucial to advancing translational research across all institutes and centers. Therefore, the Committee urges the Director to maintain core and trans-NIH support for its nationwide human tissue and organ procurement network. (p. 112)

Action taken or to be taken

NIH appreciates the Committee's recognition of the critical role of human tissues, organs, and specimens in advancing translational research. Ensuring the continued availability of human tissues and organs for biomedical research is a high priority for NIH. One of the important human tissue resource programs supported by NIH is the nonprofit organization the National Disease Research Interchange (NDRI). Since 1995, NDRI's Human Tissue and Organ Resource (HTOR) has made more than 83,000 normal and diseased tissues and organ specimens available to biomedical researchers for the study of diseases ranging from Alzheimer's disease to malaria. In 2011 alone, HTOR supplied human tissues to 420 NIH-funded and other biomedical researchers.

Six NIH Institutes and Centers (ICs) provide funds to NDRI. In addition, the NIH Office of Rare Diseases Research has provided additional funding over the past years to support the NDRI's Rare Disease Initiative for tissue distribution, researcher recruitment, source and database development, and outreach to rare diseases patient advocacy groups and their members. The NIH Office of the Director also awarded a contract in August 2010 to NDRI to provide high-quality tissues and data for the Genome Tissue Expression (GTEx) Project.

In addition to trans-NIH support, individual ICs, which are positioned to gauge specific tissue and organ needs of their researchers, provide funds for mission-specific resources. For example, NICHD supports a Brain and Tissue Bank for Neurodevelopmental Disorders, which collects,

stores, and distributes tissue samples from deceased individuals with intellectual and developmental disabilities for use by investigators.

Ensuring the supply of human tissues and organs for research purposes will remain a high priority for NIH, and we will continue to identify ways to improve the collection, storage, and distribution of tissues.

Item

Inflammatory Bowel Disease [IBD]. - The Committee commends NIH for its support of the Human Microbiome Project and notes the significance of this groundbreaking research in advancing the understanding of inflammatory bowel disease. The Committee encourages NIH to expand research in this area in collaboration with the IBD scientific community. In particular, the Committee supports expanded genetic and clinical studies of pediatric patients. (p. 112)

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has a significant inflammatory bowel disease (IBD) research portfolio that supports basic and clinical research studies of pediatric and adult IBD; the microbiota of humans and animals; and the NIDDK Inflammatory Bowel Disease Genetics Consortium, a primary driver of IBD genetics research. Two major NIDDK-supported studies were published in FY11 that show hosts' diets have profound effects on their microbiota. Both studies sequenced the total microbiota DNA (microbiome) of the hosts to determine the microbiome bacterial composition and how host diet affected these bacterial communities. Based on the results of the first study, the researchers determined that the coevolution of mammals and their microbiota is determined by host diet, not host lineage, and that the metabolic functional repertoires of microbiota can be predicted by their bacterial species composition. In the second study, researchers identified the most highly expressed bacterial genes in mice and their metabolic functions. Changes in diet affected the sizes of the bacterial communities, but not bacterial gene expression. The researchers constructed a statistical model that predicted more than 60 percent of the changes that would occur in the microbiota as a result of variations in diet.

NIDDK also has funded a planning grant for a pediatric colitis clinical study that would develop a model of clinical, genetic, and immunologic information. This model will allow clinicians to formulate individualized treatment plans for their pediatric patients to achieve clinical remission of colitis with minimal exposure to toxic medications or the need for surgery. The results of the study would be integrated with an ongoing pediatric Crohn's disease study sponsored by the Crohn's and Colitis Foundation of America.

Item

Interdisciplinary Research Consortia and the NeuroTherapeutics Research Institute. - The Committee encourages NIH to continue its initial investments in the development of the Interdisciplinary Research Consortia, in particular the NeuroTherapeutics Research Institute. (p. 112)

Action taken or to be taken

The NIH Common Fund Interdisciplinary Research (IR) Program was developed with the broad goal of changing academic research culture so that IR is viewed as a standard way of conducting research. The need for this culture change was articulated by many in the community who found it difficult to develop team approaches to complex problems because of departmental boundaries in academic institutions and because co-leadership of individual projects was not recognized or encouraged. The Common Fund IR Program therefore piloted novel award mechanisms that fostered interdepartmental, inter-institution team science and training in the institutions as well as team management within NIH. It also contributed to culture change through the recognition of Multiple Principal Investigators (PIs) on single awards.

Programs supported through the Common Fund are relevant to NIH as a whole, would not normally be supported by the NIH Institutes and Centers (ICs) because of cost and complexity, and are intended to achieve their goals within a 5-10 year time period. A major focus of the NIH Common Fund is testing new models of supporting science. The expectation for the IR Program at this stage is that successful models will be adopted by the ICs to support individual projects that are a priority for the ICs.

In FY 2007, nine IR Consortia were created under the Common Fund to test new ways to integrate different scientific disciplines to address critical health challenges and to test new ways of inter-IC management of science at NIH. Each IR Consortium addresses a unique and complex health topic. The NeuroTherapeutics Research Institute (NTRI) at the University of California focuses on the development of targeted therapies for neurological disorders through discovery of their underlying genetic and molecular causes. The NTRI team has made ground-breaking discoveries of diseases caused by mutations in a specific gene, the Fragile X mental retardation (FMR1) gene. Individual components of the consortium, led by the National Institute on Aging (NIA) and the National Institute of Neurological Diseases and Stroke (NINDS), have uncovered a possible cellular mechanism to explain how mutations in the FMR1 gene can lead to autism-like symptoms in children, and to Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) in adults, a rare condition that causes balance, tremor, and memory problems. NTRI investigators have found that subtle learning, mood, and behavioral symptoms may appear in FXTAS patients decades before overt neurological symptoms appear, suggesting that there is a much wider window of opportunity than was previously believed for preventive intervention. They also have developed new and more useful models of disease, and have identified at least three promising drug targets.

Having accomplished the goals established in FY 2007, Common Fund support for the NTRI program ended in FY 2011. NTRI investigators are well-poised to apply for continued support through the ICs either individually or through multi-PI awards.

Item

Lessons Learned. - Lessons learned with NCATS should guide NIH as it considers another proposed restructuring, one that would involve consolidating NIDA, NIAAA and components of other ICs into a new Institute devoted to research on substance use, abuse and addiction. The Committee understands that NIH plans to adopt a more deliberate approach in evaluating the

need for this Institute. The Committee strongly recommends that if the administration ultimately decides to seek such a restructuring, it should provide sufficient details in a formal budget request to Congress. (p. 85-86)

Action taken or to be taken

NIH has adopted a deliberate approach in evaluating the need for a new Institute devoted to research on substance use, abuse, and addiction. In September 2010, the Scientific Management Review Board (SMRB), pursuant to the NIH Reform Act of 2006, recommended that NIH create a new Institute focused on substance use, abuse, and addiction-related research and the dissolution of NIAAA and NIDA. The official SMRB report submitted to the NIH containing the full set of recommendations made can be found at:

http://smrb.od.nih.gov/documents/announcements/SUAA_112010.pdf.

Subsequent to receiving this recommendation, the NIH Director created a Task Force of NIH scientific leaders in consultation with subject matter experts to conduct a comprehensive review of the NIH substance use, abuse, and addiction research portfolio. Following the initial review, NIH will undertake an extensive public input process regarding the recommended proposed Institute. If NIH decides to propose this approach, it will provide a budgetary justification and details of the proposed reorganization in a future budget request to Congress.

Item

Lymphatic Research and Lymphatic Disease. - The Committee commends the trans-NIH Coordinating Committee for Lymphatic Research [CCLR] for its efforts. Nevertheless, stronger oversight and engagement is needed from the leadership of the Office of the Director and the ICs to help make more meaningful advances into the lymphatic system and lymphatic diseases, as the Committee has requested for many years. In particular, the Committee requests explicit, prospective, actionable plans and implementation strategies for each of the 2007 CCLR Working Group Recommendations that detail the prospective roles that each pertinent Institute and Center would undertake. A particular emphasis is needed on the plans for the patient registry/tissue bank; clinical and experimental imaging initiatives; the incorporation of additional expertise in lymphatic biology/disease in the pertinent CSR study sections; and the creation of programs to train new investigators in lymphatic research. Furthermore, the Committee urges NIAID and NIAMS to demonstrate greater emphasis on lymphatics. (p. 112)

Action taken or to be taken

The trans-NIH Coordinating Committee for Lymphatic Research (CCLR) continues to facilitate research on the biology and diseases of the lymphatic system and has made plans to address the following Working Group recommendations during the next several years.

Data and Biospecimens Registry: Several NIH components have existing registries with data and biospecimens that can be used for research in lymphatic biology and diseases. For example, BioLINCC houses data and biospecimens from all NHLBI-funded studies. In addition, the NIH Office of Rare Diseases Research (ORDR) is establishing the NIH Global Rare Diseases Patient Registry and Data Repository. The CCLR will work with NHLBI, ORDR, and other NIH

components having similar resources to explore opportunities to advance the efforts of the existing National Lymphatic Disease and Lymphedema Registry.

Clinical and Experimental Imaging: NIBIB, NCI, and NHLBI are supporting a number of innovative approaches in molecular and functional imaging of the lymphatic system in patients and in experimental models. NCI and NHLBI fund studies of functional imaging of the lymphatic system in patients and basic research to identify molecular targets for imaging the lymphatic system. The NCI intramural Molecular Imaging Program is collaborating with Boston Children's Hospital to adapt for use in patients an MRI agent that can image deep lymphatic anomalies in animals; they are also working to develop agents to visualize lymphatic capillaries in the body. NIBIB is supporting development of assays to detect metastasis markers and scanners for imaging cancer-detecting nanoparticles in the lymphatic system. In the third quarter of FY2012, NHLBI will issue a new translational Request for Proposals (RFP), Vascular Interventions/Innovations and Therapeutic Advances. Investigators proposing translational research in the diagnosis, imaging, and treatment of lymphatic disorders will be encouraged to submit research proposals. In addition, the CCLR is considering a re-issuance of the trans-NIH Program Announcement (PAR-07-420) to encourage research on molecular, structural, and functional imaging of the lymphatic system.

The NIH Center for Scientific Review (CSR) Study Section Expertise: Applications submitted in response to PAR-07-420 were reviewed by a special emphasis panel of experts in lymphatic biology and diseases convened by CSR. If approved for reissuance, the PAR renewal would again provide a special emphasis panel populated by experts in the field.

New Investigators: NIH has a longstanding interest in training new investigators and has been supporting research training with pre- and postdoctoral fellowships and career development awards for individuals, as well as institutional training grants. A number of investigators with training grants in the biology and diseases of the lymphatic system have successfully obtained awards as independent investigators. For example, of the two recipients of the Pathway to Independence Award (K99/R00), one has been awarded the prestigious New Innovator DP2 Award from the NIH Director's Office and the other has already applied for an R01 award during the second year of his R00 award. NIH will continue to support training of the new generation of investigators in lymphatic research using these mechanisms. Graduate students and post-doctoral researchers are also supported by the grants of established lymphatic researchers. The CCLR intends to contact current lymphatic researchers to identify the full extent of present training efforts and areas where the many NIH training mechanisms can be leveraged.

NIAMS: NIAMS continues to explore ways to collaborate with other NIH components and fund meritorious scientific research in areas relevant to its mission. Basic scientific pursuits by NIAMS-supported investigators continue to inform all areas of research, including the study of lymphatic disease. NIAID conducts and supports basic research in immunology that is advancing understanding of the lymphatic system, specific lymphatic disorders, and the roles of immunological mechanisms and inflammation in lymphatic diseases. NIAID also conducts and supports research on autoimmune lymphoproliferative syndrome, a rare immune system disorder causing accumulation of white blood cells and enlargement of the lymph nodes, liver, and spleen. In addition, NIAID conducts and supports research on lymphatic filariasis, a neglected

tropical disease caused by infectious parasites that can result in an altered lymphatic system and chronic lymphedema; this research may assist in the identification of biomarkers for lymphatic disease.

Item

Mitochondrial Disease. - The Committee appreciates the efforts of NIH to study mitochondrial function and primary mitochondrial disease. Research on primary mitochondrial disease is highly relevant to progress on a host of common diseases and conditions where mitochondrial dysfunction is clearly implicated. The Committee encourages NIH to expand its mitochondrial research portfolio to support the training of young investigators in the field and incorporate researchers with expertise in mitochondrial structure and function into the grants review and priority setting process. Finally, the Committee urges NIH to take tangible actions to implement the recommendation from NHLBI's 2007 symposium on "Modeling Mitochondrial Dysfunction" that NIH should better coordinate and share the advances that have been made by various ICs regarding mitochondrial disease. (p. 112-113)

Action taken or to be taken

The National Institutes of Health (NIH) is committed to investigating mitochondrial disease and dysfunction and provides extensive support for this area of research through targeted funding announcements and programs, individual investigator-initiated projects that address specific gaps in knowledge, and research conducted by scientists in the NIH intramural research program (IRP). The NIH research portfolio in mitochondrial disease encompasses studies ranging from basic mechanisms of mitochondrial function and disease, inherited mitochondrial disorders and disorders that are "acquired" after birth as a result of environmental factors such as diet and increasing age, and the identification of clinical markers of disease and development of new therapies.

To ensure a continued pipeline of researchers focusing on mitochondrial diseases, the National Institute of Child Health and Human Development (NICHD) provides mentored career development awards and small grant awards to new investigators who are addressing distinct clinical problems related to mitochondrial function. In addition, NICHD organized a grant preparation training session for new investigators at the United Mitochondrial Disease Foundation (UMDF) Mitochondrial Medicine 2011 annual meeting. Recently, NICHD partnered with the National Institute of Neurological Disorders and Stroke and the NIH Office of Rare Diseases Research (ORDR) to continue support for the North American Mitochondrial Disease Consortium, which is undertaking natural history studies, clinical trials, and training of new investigators in the realm of mitochondrial research. The Rare Diseases Clinical Research Network, managed by ORDR, includes an integrated international patient registry as well as a consortium for 28 mitochondrial diseases at 10 clinical centers across the United States and in Canada. Each consortium conducts integrated, multi-project and multi-institution research in rare diseases while training the next generation of rare disease researchers.

Many of the mitochondrial disease projects funded by the National Heart, Lung, and Blood Institute (NHLBI) are led by new or early-stage investigators, and more than 40 are mentored awards designed to train young investigators in the field. The NHLBI IRP has a large program

on mitochondrial biology, and of the last five new tenure-track investigators, two have specific interests in mitochondrial biology, demonstrating that NHLBI continues to build a critical mass of investigators in the field. NHLBI has also convened a number of workshops, working groups, and conferences involving national and international experts in mitochondrial research. The biennial NHLBI Mitochondrial Biology Symposium, which has become a major trans-NIH focus for mitochondrial biology, was last held in May 2011 bringing together 400 participants from around the world. The NHLBI IRP Mitochondrial Discussion Group holds monthly seminars by intramural investigators and invited speakers from the extramural community and contributes to the coordination and sharing of advances from NIH-funded mitochondrial research.

NIH is working to ensure that its pool of peer reviewers is composed of individuals with strong expertise in mitochondrial research, and NIH recently requested and received recommendations from the UMDF for scientists with relevant expertise. The information will be helpful to the Center for Scientific Review (CSR), the NIH component with primary responsibility for peer review of applications for NIH grant support, in organizing study sections. NIH has asked the UMDF to provide additional recommendations reviewers twice a year.

The ORDR has convened a working group with representatives of the NIH Institutes and Centers to coordinate the sharing of research advances to facilitate future studies and the development of better treatments for mitochondrial diseases. The working group will also include representatives from the research community and the UMDF. NIH plans a major workshop for the spring of 2012 to identify scientific opportunities and the barriers to research advances. Conclusions from this meeting will be presented at the annual scientific and patient meeting of the UMDF in the summer of 2012.

Item

Mobile Technology. - The Committee supports the new initiative by the Office of Behavioral and Social Sciences Research [OBSSR] in the area of mobile technology research to enhance health. The Committee urges that research focus on developing pilot programs to support smoking cessation, the prevention and detection of diabetes, and maternal and child health. The Committee also encourages OBSSR to engage in discussions with the Department of State and USAID to evaluate and consider global initiatives in these areas. (p. 113)

Action taken or to be taken

Mobile and wireless health (mHealth) technologies have been developing at an exponential pace in recent years. The Office of Behavioral and Social Sciences Research (OBSSR) is working with the NIH Institutes and Centers to ensure that these cutting-edge technologies are more rapidly integrated and translated into rigorously evaluated health research and healthcare tools.

OBSSR is leading the development of a new Funding Announcement Opportunity (FOA) on *Mobile Technology Research to Enhance Health*. This FOA will stimulate innovative, transdisciplinary mHealth research and will have three essential aims: 1) Translation, development, and integration of interoperable and affordable mobile and wireless technology into novel, scientifically-validated tools for use in research, healthcare, or public health; 2) Validation and implementation of the use of existing wireless and mobile devices into ongoing

clinical trials, especially those addressing treatment of chronic disease; and, 3) Development of mobile health technologies that can address infectious and noncommunicable diseases and disorders (smoking, obesity, cancer, diabetes, cardiac disease, etc.) around the world by facilitating disease prevention and behavior change.

As noted in the Committee's language, mobile health has global implications, and the areas of focus listed above have been developed in collaboration with federal domestic and international agencies. OBSSR continues to reach out and work across a wide range of federal agencies, including USAID and the Department of State, to develop research in mHealth with the greatest potential national and global health impact.

In addition to the FOA, OBSSR has sponsored a range of activities designed to help develop mHealth research capacity. In June 2011, for example, OBSSR hosted the first NIH training institute to develop multidisciplinary teams that utilize mobile health technologies to address significant health problems. This week-long training included experts from diverse scientific disciplines (medical, behavioral and social sciences, engineering, and computer sciences), as well as industry. The planning and execution of the training were done in collaboration with the Indian Health Service, Food and Drug Administration, Office of the National Coordinator for Health Information Technology, and the National Science Foundation. The training was very well received and due to demand from the global scientific community, was repeated in December 2011.

OBSSR also led a recent conference on scientific methods to improve mHealth technologies. This full day conference, co-sponsored by the Robert Wood Johnson and McKesson Foundations, included 50 scientific experts and had a webinar audience of over 300 participants. The results of the conference will be published later this fall, and the meeting video was archived to be a continued resource to the field.

Item

Mucopolysaccharidoses [MPS]. - The Committee encourages NINDS, NIDDK, NIAMS and ORDR to expand research efforts in the development of effective treatments for MPS, a group of genetic, progressive disorders that are caused by the absence or malfunctioning of certain enzymes. The Committee also urges all relevant ICs and the ORDR to fund research consortia and support conferences on MPS and lysosomal diseases. The Committee commends NINDS and the ORDR for sponsoring the recent Gordon Research Conference focusing on the basic science of lysosomal biology and function but with strong emphasis on pathogenic mechanisms of lysosomal disease. The Committee also encourages NIAMS to continue to support investigator-initiated research focused on the skeletal complications associated with MPS. (p. 113)

Action taken or to be taken

There has been a substantial increase in research on MPS in recent years. ORDR and NINDS jointly support the Lysosomal Disease Network (LDN), one of the 19 consortia of the Rare Diseases Clinical Research Network. These diseases have become a test bed for some of the most innovative and advanced experimental treatments. The combined and integrated efforts of

the lysosomal storage disease consortium focuses on 15 centers across the nation with expertise in one or more of these diseases in order to solve major challenges in diagnosis, disease management, and therapy. Currently, the clinical research and training consortium of scientists, clinicians, and patient advocacy groups supports 12 clinical studies, five of which focus directly on MPS.

In addition, the Office of Dietary Supplements (ODS) and the ORDR are developing a major initiative to guide clinical practice through evidence-based research focusing on nutrition and dietary supplement interventions that are currently used for inborn errors of metabolism (IEMs), including MPS. This effort will bring public and private stakeholders together to develop systematic approaches to investigate the safety, efficacy, and effectiveness of interventions using medical foods, special diets, or dietary supplements. The goal of this initiative is to improve clinical care and health outcomes for people with IEMs, and to serve as the basis of treatment guidelines.

Also, NINDS funds a range of both pre-clinical and clinical research aimed at treating MPS and other lysosomal storage diseases (LSDs) and to develop innovative therapeutic approaches and novel delivery methods for the treatment of LSDs, including gene therapy and stem cell transplantation. Several of these projects are readying gene therapies for clinical trials of various LSDs. For example, NINDS supports a clinical trial assessing the safety and efficacy of a gene therapy treatment for children with late infantile neuronal ceroid lipofuscinosis, a rare and fatal LSD. NINDS is funding experts from the Tay-Sachs Gene Therapy Consortium, a collaboration of four institutions in another preclinical assessment of gene therapy. As a novel approach to the treatment of MPS, NINDS-funded investigators are developing small molecule drugs that stimulate the breakdown of carbohydrates that build up in the cells of MPS patients, bypassing the need for lysosomal enzymes altogether. In addition to the Gordon Research Conference on lysosomal biology and function, NINDS also funded the 6th Annual World Symposium on LSDs.

NIDDK supports a number of research projects to determine whether transposons containing therapeutic genes can cure MPS disease in dog models for human gene therapy and to analyze all treated MPS VII dogs long-term for the efficacy and safety of gene therapy. If successful, this study should hasten the development of a simple and effective treatment for reducing or preventing the devastating clinical manifestations of MPS VII and lead the way for treating other LSDs.

NICHD currently funds three innovative gene therapy projects focused on MPS type 1, extending through the next 5 years. Animal data from one project has established a proof of principle for gene therapy in a mouse model of MPS1. Other research is building upon this success by testing better gene therapy vehicles and brain delivery strategies, using multiple animal models as well as primary brain cells and tissues. A third project will test a highly-innovative “cut and paste” strategy to correct the genetic defect in the chromosomes of MPSI mice.

NIAMS has recently funded a project by a new investigator that will study bone health, skeletal growth, and endocrine function, as well as the impact of human growth hormone treatment, in a group of children with MPS. In collaboration with NINDS, this project will also build a registry

of patients with these pediatric diseases that follows their growth and development, and characterizes their bone and endocrine disease phenotypes. In addition to the scientific aims, this NIH Mentored Patient-Oriented Research Career Development Award will serve to accelerate the career development of a young clinician scientist interested in pediatric metabolic bone disease research through mentored activities to develop independent research skills.

Item

Neurofibromatosis [NF]. - NF is an important research area for multiple NIH institutes. As NF is connected to many forms of cancer in children and adults, the Committee encourages NCI to substantially increase its NF research portfolio in pre-clinical and clinical trials by applying newly developed and existing drugs. The Committee also encourages NCI to support NF centers, clinical trials consortia, patient databases, and biospecimen repositories. The Committee urges additional focus from NHLBI, given NF's involvement with hypertension and congenital heart disease. Because NF causes tumors to grow on the nerves throughout the body, the Committee urges NINDS to continue aggressive research on nerve damage and repair. In addition, the Committee continues to encourage NICHD and NIMH to expand funding of clinical trials for NF patients in the area of learning disabilities. Children with NF1 are prone to the development of severe bone deformities, including scoliosis; the Committee therefore encourages NIAMS to expand its NF1 research portfolio. The NIDCD is urged to expand its research on NF2, which accounts for approximately 5 percent of genetic forms of deafness. The Committee encourages the NEI to support research on the treatment of optic gliomas, vision loss and cataracts, major clinical problems associated with NF. Finally, the Committee encourages NHGRI to expand its NF portfolio, as NF represents an ideal model to study the genomics of cancer predisposition, learning and behavior, and bone disease. (p. 113-114)

Action taken or to be taken

NCI actively collaborates with other institutes and outside organizations to advance NF research through a variety of mechanisms, including co-funding research on NF and supporting scientific conferences and planning meetings for a range of research on NF and similar diseases. NCI also participates in Children's Tumor Foundation conferences, which have brought international NF researchers and physicians together and contributed to the significant advances in NF research in recent years. NCI participates in a leadership role in the Department of Defense-sponsored NF Consortium, a group of nine sites across the country that aims to accelerate the development and conduct of NF clinical trials.

In the past year, NCI researchers have made progress in developing new therapies for NF1-associated cancers, demonstrating that a lab-synthesized version of schweinfurthin, a product isolated from the leaves of a Cameroonian plant, can inhibit the growth of peripheral nerve sheath tumors in living animals. They have also identified other natural products that inhibit NF1-associated astrocytomas. Existing molecularly targeted therapies such as Rapamycin, Lovastatin, Avastin are being evaluated for NF treatment. NCI researchers recently initiated a Phase I clinical trial of AZD6244, a new drug that inhibits a key pathway of tumor formation, for pediatric patients with NF1 and inoperable pre-malignant lesions. In addition, NCI has established one of the largest clinical trials programs for children and young adults with NF1,

including treatment and natural history trials which comprehensively evaluate NF1-related manifestations.

In 2010, NCI conducted the first genome-wide association study (GWAS) to identify genes related to NF1 and to sequence NF1-associated tumors. Genes other than NF1 have been shown to play a role in the wide variability of disease severity seen in NF1, and an important goal of current research efforts is to understand how these genes work.

NHLBI will work with other Institutes to incorporate neurofibromatosis into existing and future cardiovascular, pulmonary and hematologic research.

NINDS funds projects investigating the mechanisms underlying the development of tumors in NF with the goal of developing non-surgical methods for preventing tumor growth, which would also prevent nerve damage caused by NF tumors. Additionally, NINDS-funded researchers are investigating the mechanisms underlying nerve degeneration and neuropathic pain, both of which can occur after nerve damage, and are investigating ways of promoting nerve regeneration or surgically repairing damaged nerves.

Through its support of the University of Alabama-Birmingham (UAB) Intellectual and Developmental Disabilities Research Center (IDDRC), NICHD is participating in the Department of Defense-funded Neurofibromatosis Consortium, a group of nine clinical sites with an overall goal of developing effective, innovative therapies for children and adults with NF. The UAB IDDRC Administrative and Biostatistics Core provides support for the consortium in the form of clinical trial development, data management, and statistical analysis, and its Developmental Genomics core provides mutation analysis of individuals with neurofibromatosis. Among the clinical trials being pursued as part of this consortium is a trial examining the use of lovastatin, a cholesterol-lowering drug, to improve cognitive outcomes in children with NF1 and learning disabilities.

NIMH supports an exploratory intervention trial to examine whether lovastatin treatment can attenuate learning and attention deficits of children ages 10-18 with NF1. The study is evaluating whether lovastatin treatment improves real-world outcomes (e.g., school function and patient/teacher reports). In the study, 60 children are being randomly assigned to a placebo (sugar pill) or treatment group. Over the course of 14 weeks, the children are treated and then given follow-up assessments at 18 weeks. In addition, functional neuroimaging is being performed pre and post treatment in order to investigate the neural mechanisms underlying cognitive changes associated with lovastatin treatment.

NIAMS continues to explore ways to collaborate with other NIH Institutes and Centers and fund meritorious scientific research in areas relevant to its mission. In addition, basic scientific pursuits by NIAMS-supported investigators continue to inform all areas of research, including the study of NF.

NIDCD supports research on NF2 in its extramural and intramural research programs. NF2 is an inherited genetic disorder typically characterized by bilateral vestibular schwannomas (benign nerve tumors), which grow in the auditory-vestibular nerve that travels from the ear to the brain.

The tumors can damage the nerve and lead to deafness and chronic imbalance. The current treatment is surgical removal of the tumors, however, the surgery may further damage the nerve, and the optimal timing of intervention and the most appropriate therapy are not well defined.

NIDCD-supported scientists are exploring vestibular schwannomas to better understand the causes of NF2 tumor formation and progression, and identify novel therapies that limit schwannoma growth. In collaboration with NINDS and other NIH institutes, NIDCD intramural scientists and clinicians are conducting a clinical natural history study to examine the growth rates of vestibular schwannomas, and the auditory and vestibular function of people with NF2. These studies will further our understanding of the most appropriate therapy and the optimal timing of intervention for this disorder. Another collaborative study between NIDCD, NCI, and NINDS intramural scientists has shown that the biologic agent bevacizumab has been shown to stabilize tumor growth and improve hearing outcomes for select symptomatic vestibular schwannoma NF2 cases. NIDCD intramural scientists are examining the effect of bevacizumab on both auditory and vestibular function.

Previous studies of NF2 found that more than 90 percent of patients develop eye lesions. The most common eye complication in NF2 is the juvenile cataract (opacity of the lens). NEI has an entire research program dedicated to understanding the biological mechanisms that lead to cataract formation. Learning more about this process will help better understand the development of cataracts in NF2. NEI also contributed funding for a NF conference held in 2011 and hosted by NINDS.

NF is a useful model through which to study the genomics of cancer predisposition. NHGRI is committed to understanding the molecular basis of cancer through the application of genome analysis technologies and continues to support a portfolio of large-scale genome sequencing. In follow-up to our recently published strategic vision for genomics, which includes an explicit call to pursue genomic advances in cancer, NHGRI is developing plans for its research portfolio over the next three to five years that will include considerations of diseases such as NF.

Item

OppNet. - The Committee encourages NIH to continue its support of the NIH Basic Behavioral and Social Science Opportunity Network [OppNet] and requests an update on the network's progress in the fiscal year 2013 congressional budget justification. (p. 114)

Action taken or to be taken

Per the Committee's request for an update, OppNet is an NIH-wide initiative in the basic social and behavioral sciences that funded 47 grants in Fiscal Year (FY) 2011 at a total of \$10,664,857. This amount exceeds its original plan for a pooled \$10 million from 24 NIH Institutes and Centers; because of high enthusiasm for the program, additional voluntary donations were provided by 10 Institutes, Centers, and program offices (within NIH's Office of the Director) that allowed OppNet to exceed its goal. Major scientific areas include the self-regulation of behavior, the influence of the social environment on basic behavioral mechanisms, reliable and valid measures of psychosocial variables associated with sleep and the social environment, and reliable and valid measures of psychosocial and physiological processes associated with stress.

Topics for the grants' funding opportunity announcements emanated from OppNet's October 2010 conference for researchers, advocates, and other interested parties to recommend research areas on fundamental social and psychological processes related to health and well-being.

In FY 2011, OppNet also funded grants to build future research capacity among the basic social and behavioral sciences including conference grants designed to build new interdisciplinary research teams, curriculum development to enhance the careers of earlier stage researchers, and mentoring grants for mid-career and senior investigators who seek training in OppNet's target areas or basic behavioral and social scientists who require training in additional areas. All FY 2011 OppNet projects are listed on its website (<http://oppnet.nih.gov/resources-2011fundedapp.asp>) to facilitate swift access to OppNet efforts while it ensures the diffusion of this research throughout the entire agency.

To increase the awareness and understanding of OppNet's scientific areas across NIH, OppNet initiated a symposium series, Human and Model Animal Research in the Behavioral and Social Sciences, to bring together scientists who conduct research on similar topics. Each symposium pairs a presentation by at least one researcher who studies human subjects and another who studies a complementing animal model. Presenters have included both NIH intramural and university-based scientists. After individual presentations, the presenters, moderators, and symposium participants discuss areas of interest and potential future research needs and opportunities. Three symposia have been held to date; all presentations and materials are recorded and available to the public through OppNet's website (<http://oppnet.nih.gov/news-symposium.asp>). Live symposia occur in the NIH Clinical Center's Lipsett Amphitheater to provide a central NIH location for employees and visitors. Public access to videocasts allows OppNet to disseminate this research to as many interested parties as possible. Additional dissemination occurs through OppNet's Facebook and Twitter accounts (<http://www.facebook.com/pages/OppNet-NIHs-Basic-Behavioral-and-Social-Science-Opportunity-Network/170821026294528>; <http://twitter.com/#!/nihoppnet>).

Item

Overlapping Chronic Pain Conditions. - The Committee recognizes that NIH has taken seriously its repeated calls for an improved and expanded research effort to better understand overlapping chronic pain conditions including chronic fatigue syndrome, endometriosis, fibromyalgia, headache, interstitial cystitis, irritable bowel syndrome, temporomandibular joint and muscle disorders, and vulvodynia. As noted by the IOM report on pain released in June, these poorly understood and neglected conditions impact 50 million American women and cost the Nation \$80,000,000,000 annually, an amount that could be substantially reduced with improved research, education and care. The Committee is aware that initial progress is being made toward the development and implementation of a trans-NIH research initiative to support studies aimed at identifying etiological pathways of these overlapping conditions, with the goal of identifying potential therapeutic targets, and expects further substantial progress to be made this fiscal year. This will require continued and expanded efforts by all the relevant ICs. The Committee urges NINDS to take the lead on this effort. (p. 114)

Action taken or to be taken

The National Institutes of Health (NIH) recognizes the heavy burden these poorly understood chronic pain conditions place on patients, especially women, and it is actively supporting efforts to advance the understanding and diagnosis of these conditions and address their frequent overlap. In 2011, NIH hosted a number of meetings and workshops which included discussions of possible common etiological pathways underlying many of these conditions. In April 2011, the Office of Research on Women's Health (ORWH), in collaboration with the Trans-NIH **Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Working Group**, hosted a *NIH State of Knowledge Workshop on ME/CFS* to review and discuss the opportunities and gaps in advancing science for ME/CFS research. The *6th Annual NIH Pain Consortium Symposium*, also held in April 2011, focused on the mechanisms and management of overlapping chronic pain and associated conditions. In June 2011, the National Institute for Dental and Craniofacial Research (NIDCR) provided support for the *6th Scientific Meeting of the TMJ Association* which focused on the mechanisms, diagnosis, and treatments of temporomandibular joint disorders and co-morbid chronic pain conditions. In July 2011, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) sponsored a scientific research agenda setting meeting to facilitate increased research in vulvodynia. A research plan listing priorities for vulvodynia as a chronic pain condition is expected to be published in early 2012. A common theme which emerged from these conferences was the need for improved research diagnostic criteria (RDC) for overlapping pain conditions. Such criteria establish an evidence-based diagnostic and classification system to aid in the rational choice of clinical care and allow for reliable research data to be generated. The process to establish these criteria could be modeled on current NIH efforts such as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-supported **Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Syndromes Research Network** which is addressing key clinical questions in interstitial cystitis/painful bladder symptoms and chronic prostatitis/chronic pelvic pain syndrome and potential links with CFS, fibromyalgia, and irritable bowel syndrome.

Recognizing that a coordinated research agenda may facilitate progress in ameliorating the burden of these diseases, a new trans-NIH overlapping chronic pain conditions working group was formed in fall 2011. Led by the National Institute of Neurological Disorders and Stroke (NINDS) and NIDCR, it brings together program directors from 13 Institutes and Centers involved in pain research as well as representatives from patient advocacy groups. The group will assure coordination of research efforts across NIH on overlapping chronic pain conditions and it will also plan and support a trans-NIH conference that aims to (1) evaluate current knowledge on the causes and progression of overlapping pain conditions, (2) identify critical research needs, such as improved RDC, and (3) enhance interdisciplinary collaboration.

In addition, NIH has engaged with diverse stakeholders to discuss current needs in chronic pain research and is promoting increased awareness of overlapping conditions. For instance, NINDS along with staff from NIDCR, NICHD, ORWH, and NIDDK met with representatives from the Chronic Pain Research Alliance in October 2010 and August 2011 to discuss the present state of research and future priorities in overlapping chronic pain conditions. NIH communication materials on chronic pain conditions now reference other overlapping conditions, while initiatives such as the NIDCR institutional career award for TMJD research which were

originally designed for individual pain conditions, now acknowledge the possible overlap with other conditions as an important research question.

Item

Overview. - The Committee regrets that fiscal constraints prevent a higher recommendation funding level for NIH. With tight budget likely to continue for the foreseeable future, the Committee strongly urges NIH to explore creative ways to rethink the way it allocates its funding. The alternative--continuing to nick away, little by little, at the success rate or the size of awards – will inevitably have a negative impact on young investigators, who represent the Nation’s future, and on high-risk, high-reward research opportunities. (p. 84-85)

Action taken or to be taken

NIH agrees with the Committee and is in the process of evaluating its research portfolio and grants policies to eliminate duplication, and continue to focus resources on early-stage investigators (ESIs) and highly innovative research.

In October 2011, NIH made data available regarding the analysis of several options for supporting more highly-innovative research, focusing on support for ESIs. NIH is collecting input from the research community on the various approaches outlined in the data.

In the meantime, NIH is beginning to implement policies to accomplish these goals. In its FY 2012 fiscal policy for grant awards, which was announced in January 2012, NIH established a policy of not providing inflationary adjustments for grants and avoiding growth in the average size of awards. These policies will help NIH to fund an increase in the number of new and competing grants in FY 2012 and FY 2013.

The FY 2013 Budget expands upon these efforts. Applications from principal investigators (PIs) who already receive in excess of \$1.5 million per year in total costs would be triggered for additional scrutiny and review by the IC Advisory Council. While this policy will not change the total number of awards, it will likely increase the total number of PIs supported by NIH.

NIH will also continue to make funding ESIs a priority. NIH will continue its policy of funding applications from ESIs at the same success rate as established investigators for new R01 equivalent applications. Additionally, NIH will continue to support new and early stage investigators with specific programs targeted to these career stages: the NIH Director’s New Innovator Award, the Pathway to Independence Award, and the NIH Director’s Early Independence Award. NIH will also continue to support highly innovative research with the NIH Director’s Pioneer Award and the NIH Director’s Transformative Research Award.

Item

Pain. - The Committee has for many years encouraged a stronger emphasis on pain research at NIH, and so it notes with great interest the recent Institute of Medicine report "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." The report, which was mandated by the Patient Protection and Affordable Care Act and funded by NIH,

estimates that chronic pain afflicts at least 116 million adults in the United States and costs the Nation between \$560,000,000,000 and \$635,000,000,000 a year, of which \$99,000,000,000 is borne by the Federal Government and States. The report documents the growing recognition that chronic pain can be a disease in itself, causing changes throughout the nervous that often worsen over time. Nevertheless, the biological and psychological aspects of pain, as well as its diagnosis, treatment and prevention, remain poorly understood. NIH took a first step toward addressing these questions in a systematic way by creating the NIH Pain Consortium in 2003. Eight years later, it is clear that NIH must do more. Although every Institute and Center deals in some way with pain, none of them "owns" this critical area of research. If that is to be responsibility of the Pain Consortium rather than an individual IC, then the consortium needs more resources, more staffing and a more elevated status within NIH. The IOM report concludes that "there needs to be a transformation in how pain research is conducted and that the Pain Consortium should take an even more proactive role in effecting that transformation." In addition, the report recommends that the consortium should hold "more frequent, regular, structured and productive meetings" and improve the process for reviewing grant proposals related to pain, and that NIH should consider the possibility of identifying a lead IC on pain. The Committee requests a response to the IOM recommendations in the fiscal year 2013 congressional budget justification. (p. 114-115)

Action taken or to be taken

The NIH Pain Consortium was established to enhance pain research and promote collaboration among researchers across the 23 NIH Institutes, Centers, and Offices that have programs and activities addressing pain. In 2010-2011, the Consortium was proactive in supporting a number of pain research initiatives and activities at NIH which included identifying key opportunities in pain research and education, convening conferences and workshops to highlight recent advances and needs in the field, and building collaborations with other federal agencies and academic institutions involved in pain research. The Pain Consortium is also catalyzing a number of efforts that address issues raised in the IOM report on pain. As a reflection of this enhanced activity level, the Pain Consortium moved to a more frequent quarterly meeting schedule.

In April 2011, the Pain Consortium sponsored its 6th Annual Symposium focusing on *Mechanisms and Management of Overlapping Chronic Pain and Associated Conditions* which focused on the underlying neurological mechanisms and psychosocial factors that may contribute to co-morbid pain conditions, as well as treatment strategies and obstacles to managing these overlapping pain conditions. In September 2010, the NIH Pain Consortium sponsored a workshop led by the National Institute of Aging (NIA) to identify research priorities for improving pharmacological management of chronic pain in older adults in clinical settings. NIH and the FDA plan to hold a state of the science workshop related to opioid efficacy in conjunction with the 7th Annual NIH Pain Consortium Symposium in 2012. In addition, members of the NIH Pain Consortium currently participate in an advisory committee for the Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTION) initiative, a public-private partnership program sponsored by FDA to streamline the discovery and development of analgesics.

Led by the National Institute on Drug Abuse (NIDA), the Pain Consortium plans to launch nine NIH Pain Consortium Centers of Excellence (COE) for Pain Education focusing on pain education in medical, nursing and dental schools in late 2011. The COE are designed to address

the urgent need for pain education, highlighted in both the IOM report and the President's 2011 action plan to address the national prescription drug abuse epidemic. The Centers will provide resources to coordinate a broad pain education initiative across the nation while leveraging existing expertise in academic institutions.

Finally, the NIH Office of the Director designated the National Institute of Neurological Disorders and Stroke (NINDS) as the lead institute for pain research at NIH. In this new role, the NINDS Director, currently a member of the Pain Consortium Executive Committee, would become the Chair of the committee, and would work to catalyze and coordinate enhanced trans-NIH research efforts on pain. NINDS plans to establish a two person office to support all activities related to the Pain Consortium and the Interagency Pain Research Coordinating Committee (IPRCC). The IPRCC was recently created under the Patient Protection and Affordable Care Act to enhance pain research efforts and promote collaboration across the government, advance fundamental understanding of pain and improve pain-related treatment strategies. NINDS has been actively involved in coordinating many of the Pain Consortium activities to date as well as establishing both a new trans-NIH working group on overlapping chronic pain conditions and the IPRCC.

Item

Pediatric Low-Grade Astrocytoma [PLGA]. - The Committee understands that current treatments for PLGA, a slow-growing children's brain cancer, are invasive, toxic and largely ineffective, and have not advanced in almost 25 years. Therefore, the Committee urges NCI, NINDS, NIBIB, and ORDR to accelerate the pace of expansion of the pediatric cancer research portfolio by creating research priorities with a sequential agenda and timeline, and facilitating the collaboration of organizations (both public and private) already funding related research initiatives. The Committee further encourages the institutes to prioritize targeted translational research projects that will help identify chemical compounds or combination therapies for use as more effective, less toxic treatments. The Committee requests an update on these efforts in the fiscal year 2013 congressional budget justification. (p. 115)

Action taken or to be taken

Major advances in understanding the biology of PLGA have been achieved over the past five years, and because of these advances, clinical research teams are now poised to translate these findings into new therapeutic options. The most significant research advance, supported in part by NCI, is the recognition that the vast majority of PLGA cases have genomic alterations involving a gene called BRAF. This advance has enabled the development of preclinical models which will, in turn, support research on promising candidate treatments.

NINDS supports studies to carefully dissect the molecular and cellular underpinnings of PLGA, including funding the development of a new BRAF mouse model to be used for pre-clinical therapeutic testing. These studies, in conjunction with discoveries from the NIH Cancer Genome Atlas, which analyzes the complete genomes of various cancer types, should enable scientists to better identify different subtypes of astrocytoma. NINDS supports several therapeutic development initiatives, including a translational research program and the trans-NIH

Neurotherapeutics Grand Challenge, which encourage proposals for the development of novel drugs for all neurological disorders, including PLGA.

The NCI-supported Pediatric Preclinical Testing Program developed a model for a subtype of PLGA with the BRAF mutation and identified a targeted therapy, selumetinib (AZD6244), for additional research. Currently, the NCI-supported Pediatric Brain Tumor Consortium (PBTC) is conducting a Phase I trial of selumetinib in children with PLGA who have progressed after receiving radiation therapy. In other efforts focused on neurofibromatosis-associated PLGA, NCI researchers screened thousands of existing drugs and new compounds isolated from plants and marine life for potential therapeutic activity for PLGA.

The NCI-supported Children's Oncology Group (COG) recently completed a Phase III study comparing two combination chemotherapy regimens for PLGA, and also has completed enrollment for a Phase II study evaluating the efficacy and toxicity of specialized radiation therapy that delivers radiation directly to the tumor and reduces radiation to normal tissue. Final results for both studies are pending. Future studies for children with PLGA include a COG trial of lenalidomide, a novel immunomodulator, planned for 2012. NCI is also conducting and supporting research on optimal imaging methods for assessment and monitoring of PLGA disease status.

NIBIB is supporting the development of multifunctional drug and gene delivery systems. Such systems can target therapies to particular cells and intracellular compartments in the affected tissue, including brain, and can monitor drug delivery and therapeutic efficacy using advanced imaging and/or sensing technologies. This approach has potential to reduce treatment toxicity while increasing efficacy.

Item

Primate Research. - The Committee continues to support the National Primate Research Centers, which allow NIH-supported scientists to conduct nonhuman primate research in the pursuit of improving human health. (p. 115)

Action taken or to be taken

The National Primate Research Centers (NPRC) provide the infrastructure and expertise for investigators using nonhuman primates (NHPs) in biomedical research. Major research areas in FY 2011 included infectious diseases, such as HIV-AIDS and malaria; neurodegenerative diseases such as Parkinson's and Huntington's diseases; reproductive and developmental biology; and metabolic diseases such as diabetes. In FY 2011, the NPRC housed approximately 27,500 NHPs and supported approximately 1,000 projects involving 2,300 investigators. In addition to service to the research community, the NPRC continue to emphasize consortium-based activities that improve efficiency, avoid redundancy, and reduce operating costs.

Item

Product Development Partnerships. - Public-private partnerships, including product development partnerships [PDPs], can both enable critical research and development in the

global health arena and create jobs in the United States. The Committee encourages NIH to cultivate PDPs and to work with CDC and other agencies that have a role in advancing global health to identify and pursue other innovative research and development opportunities. (p. 115)

Action taken or to be taken

In response to the increased dependence on globally-derived datasets and international multi-site trials to promote discovery and the translation of knowledge into cures, NIH has partnered with private, non-profit, and government institutions to advance public health around the globe. Product development partnerships (PDPs) formed directly with the private sector include the “UnitedHealth and NHLBI Collaborating Centers of Excellence” network, through which the National Heart, Lung, and Blood Institute (NHLBI) has awarded ten contracts to institutions in low- and middle-income countries to support research surrounding interventions for non-communicable diseases. The National Institute on Allergies and Infectious Diseases (NIAID) is a partner in the “Lilly TB Drug Discovery Initiative,” to which Eli Lilly recently pledged an additional \$30 million to help fight multidrug-resistant tuberculosis in developing countries. Through partnerships with pharmaceutical companies, the National Cancer Institute (NCI) has placed promising new drugs such as sorafenib and temsirolimus into recent clinical trials for liver cancer, which is the most common cancer in some parts of the world, such as Sub-Saharan Africa and South East Asia. The National Institute of Drug Abuse (NIDA) has made initial awards for a Product Development Partnership entitled “Medication Development for Tobacco Dependence (MITD)” to accelerate the development of more effective and accessible anti-smoking medications by leveraging collaboratively the strengths and resources of public, non-profit, and private-sector organizations through phased UH1 and UH2 awards commencing in FY 2011.

NIH Institutes and Centers have also been able to work jointly with non-profit entities, which have played an increasingly important role in research on diseases that affect populations in developing countries. The Foundation for NIH and the Fogarty International Center (FIC) entered into a partnership with the Bill & Melinda Gates Foundation (\$30 million over five years) to conduct longitudinal studies in least developed countries on the global pattern of nutritional and enteric disease factors influencing early childhood development.

Working with other Federal agencies, NIH has undertaken a number of activities that leverage existing resources and expertise. FIC has a long-standing International Cooperative Biodiversity Groups Program focused on natural product development, and current Federal agency partners include the National Science Foundation, Department of Energy, Department of Agriculture and the National Oceanic and Atmospheric Administration. In addition, the FIC International Training and Research in Environmental and Occupational Health program is cost-shared with the Centers for Disease Control and Prevention (CDC).

NIH continues to develop new opportunities for public-private partnerships. For example, NIAID and the National Institute of Mental Health (NIMH) have established the Martin Delaney Collaboratory, which will allow grantees the opportunity to design, develop and evaluate new strategies for curing HIV infection through partnerships among government, industry, and academia. In addition, the NIH Common Fund is partnering with the Wellcome Trust and African Society of Human Genetics to establish H3Africa, a program that will support

population-based genetic studies on common, non-communicable disorders as well as communicable diseases. This program is also helping to build infrastructure to allow research to occur in Africa.

Item

Rehabilitation Research. - The Committee recognizes the need to continue to build a sustainable infrastructure and capacity of emerging scientists in rehabilitation research. The Committee encourages the use of career development awards for emerging scientists, such as physical therapists, to meet this need. (p. 115)

Action taken or to be taken

The National Center for Medical Rehabilitation Research (NCMRR) within NICHD is working on an ongoing basis to attract, mentor, and fund applications from new researchers in the field of rehabilitation research. The NCMRR staff actively promotes research opportunities at professional meetings, and seeks out newly-independent rehabilitation clinicians and physical therapists to provide them with information on career development, research support, grantsmanship, and the NIH peer-review process.

In addition to supporting individual K01 career development awards, which NICHD targets to rehabilitation researchers, NCMRR also supports two highly-successful programs (using the K12 mechanism) that provide a national network of mentorship and career development for rehabilitation professionals. These programs are targeted specifically to both physicians and physical and occupational therapists, and have produced outstanding scientists in rehabilitation research. For example, within three years of entering the program, one scientist already has obtained multiple NIH grants, including a large grant award (R01), and was awarded the 2009 Excellence in Research Award from the *Journal of Orthopaedic & Sports Physical Therapy* for his work examining interactions among biology and psychology in patients with carpal tunnel syndrome. Another outstanding scientist trained by NCMRR's rehabilitation career development programs not only obtained several NIH grants, but also received numerous awards for his pioneering research, including the 2008 Presidential Early Career Award for Scientists and Engineers and the 2010 Outstanding Neurorehabilitation Clinician Scientist Award from the American Society of Neurorehabilitation.

Item

Spina Bifida. - The Committee encourages NIDDK, NICHD and NINDS to study the causes and care of the neurogenic bladder to improve the quality of life of children and adults with spina bifida; to support research to address issues related to treatment, management and associated secondary conditions, such as hydrocephalus; and to invest in understanding the myriad co-morbid conditions experienced by children with spina bifida, including those associated with both paralysis and developmental delay. (p. 115)

Action taken or to be taken

NICHD is committed to improving the outcome of children with spina bifida. The recently completed Management of Myelomeningocele Study (MOMS) clinical trial demonstrated that

prenatal repair of the defect, before 26 weeks of pregnancy (compared to the standard postnatal surgery), dramatically improved health outcomes for the baby, including reducing the need for a ventriculoperitoneal shunt by one-third, reducing the presence of hindbrain herniation at 12 months by one-third, and doubling the number of children who could walk independently at 30 months. However, the trial also showed significant risks, including premature birth (occurring in 80 percent of those undergoing prenatal repair), and a thinning or opening of the hysterotomy incision at the time of cesarean delivery in over one-third of the women, which also poses a risk for subsequent pregnancies. Supported by NICHD, MOMS trial investigators have planned extensive follow-up bowel and bladder assessments of the children in the trial, including the need for intermittent catheterization or further surgery at 30 months; these analyses are ongoing. In addition, the investigators plan to use appropriate infant development scales to evaluate the presence of developmental delays or paralysis, and will work with certified physical therapists to determine the children's level of motor function.

NICHD supports other basic, translational, and clinical research on spina bifida including a long-term longitudinal study on the impact of this condition on cognitive development and function, and on brain connectivity patterns as revealed by magnetic resonance spectroscopy. Other studies involve the amelioration of sensory motor deficits using specific exercise regimens. These studies also provide insight into other physical and psychosocial co-morbidities that accompany spina bifida and change over time as children with spina bifida grow and reach adolescence.

NINDS also supports research related to the causes of spina bifida and other neural tube defects, and on interventions and treatments for associated secondary conditions, including hydrocephalus. While shunts to drain excess cerebrospinal fluid are the most common treatment for hydrocephalus, difficulties in monitoring fluid accumulation to prevent shunt blockages and infections negatively affect the quality of life in people with this condition. NINDS-funded projects aimed to improve shunt monitoring are identifying a non-invasive biomarker to quantify injury and recovery, designing a sensor for measuring brain ventricle volume, and developing an ambulatory monitoring system for detecting shunt failure. NIH continues to support the Hydrocephalus Clinical Research Network, a multi-site network that is working to develop quality improvement measures, build a patient registry, and improve the diagnosis and treatment of pediatric hydrocephalus.

NIDDK recognizes the burden of bladder complications for people with spina bifida, especially pediatric neurogenic bladder. NIDDK supports research into nervous system-based bladder function and dysfunction, such as overactive bladder and urinary incontinence, as well as research on bladder tissue regeneration, which may yield new therapeutic approaches helpful to people with spina bifida. Moreover, NIDDK is supporting basic research studies of how proper nerve connections are established in the bladder and lower urinary tract during early life development, which may contribute to greater understanding and improved treatment of neurogenic bladder from spina bifida and other causes. Together, these lines of research could lead to quality-of-life improvements for children and adults with spina bifida.

Item

Tuberous Sclerosis Complex [TSC]. - The Committee continues to encourage additional research on TSC and related neurological disorders. Because TSC serves as a gateway for understanding more prevalent neurological disorders such as autism and epilepsy, the Committee encourages NIH to focus resources on clinical trials for new drug targets for TSC. (p. 115)

Action taken or to be taken

Tuberous sclerosis complex (TSC) is an important area of research at NIH, where several Institutes are working to advance knowledge of its cause and treatment and how its molecular underpinnings may relate to other neurological disorders. For example, research funded by the National Institute of Neurological Disorders and Stroke (NINDS) indicates that the TSC1 and TSC2 genes and their related molecular signaling pathways are important for brain development and regulating the connections between neurons and/or astrocytes. Autism and epilepsy are thought to arise from abnormalities in brain development and dysfunction of the connections between neurons, suggesting that TSC1 and TSC2 gene products (i.e., proteins) may be involved in non-TSC forms of epilepsy and autism. NINDS continues to fund research investigating the role of TSC1 and TSC2 genes and their related pathways in brain development and neural signaling to provide new insights into the mechanisms underlying epilepsy and autism. Using Recovery Act funds, NINDS is funding the development and characterization of animal models that will enable researchers to increase understanding of how TSC1 and TSC2 proteins interact with proteins encoded by genes associated with autism. In addition, NINDS funds research to determine mechanisms of epileptogenesis in TSC and whether these mechanisms also contribute to epileptogenesis in non-TSC models of epilepsy.

NINDS is committed to testing new drugs for neurological disorders, including TSC, and has recently created the Network of Excellence in Neuroscience Clinical Trials (NeuroNEXT) Program as a standardized infrastructure for conducting early stage clinical trials for neurological disorders affecting adult and/or pediatric populations. The Program encourages proposals for the testing of novel drugs for all neurological disorders, including TSC. NINDS also contributed funds to the TS Alliance's "Summit on Drug Discovery in Tuberous Sclerosis Complex and Related Disorders," which was held in June 2011 to provide a forum for discussing ongoing translational and clinical research in TSC and planning future efforts in these areas.

The lack of knowledge about the specific neural mechanisms responsible for neurocognitive and neurobehavioral deficits in autism spectrum disorder (ASD), including those co-occurring in neurodevelopmental disorders such as TSC, remains a significant obstacle. NIMH funds studies that explore basic molecular pathways and genetic mouse models of TSC to determine how abnormalities in molecular mechanisms give rise to cognitive and behavioral anomalies seen in ASD. Knowledge gained from these studies may, in turn, lead to potential therapeutic interventions for individuals with ASD. Funded research also seeks to develop better ways to image the living brain in children with ASD (including those with TSC), which will enable dramatic improvements in our capacity to chart the natural history of these disorders over the lifespan.

TSC1 and TSC2 are part of the mTOR signaling pathway which is involved in the regulation of protein translation and cell growth. Several NIAMS-funded researchers are working to increase

understanding of this pathway and its involvement in normal cellular processes and abnormal conditions and diseases. A better understanding of the mTOR pathway will provide additional targets for drug intervention in TSC, as well as a better understanding of how mutations in TSC1 and TSC2 lead to abnormalities in multiple organ systems.

Item

Vulvodynia. - The Committee notes that educational materials developed as part of the vulvodynia educational campaign have not been made available to key audiences and urges ORWH to widely disseminate them to federally funded health centers and college health clinics, as well as to the public and patient and medical communities. (p. 115)

Action taken or to be taken

The Office of Research on Women's Health (ORWH) has supported a variety of initiatives to expand and enhance vulvodynia research and education. Some initiatives have been long-standing, including several trans-NIH collaborations. ORWH continues to partner with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to update and distribute *Vulvodynia Awareness Campaign* (VAC) materials, which include reprints of major research reports and information for women who may be suffering from vulvodynia, such as resources for clinical evaluation and follow-up. These materials also were distributed at a July 2011 NIH-sponsored research meeting aimed at developing a research plan for vulvodynia. Meeting participants urged NIH to continue its dissemination efforts of these and other educational materials.

In collaboration with the National Library of Medicine (NLM), ORWH developed a primary women's health educational resource called the *Women's Health Resources Web Portal* (<http://www.womenshealthresources.nlm.nih.gov/>). This resource will be a dissemination point for research findings on vulvodynia to researchers, health care providers, and consumers. Also VAC educational materials will be updated and made available digitally through the Portal. In addition, the Portal utilizes Twitter and Facebook, which can be used for tailored messaging to reach a wide audience of health professionals and consumers. A toolkit of resources will be developed for college health clinics that will include educational awareness materials, consumer materials, and targeted messaging that can be used in health campaigns and outreach through social media. The initial toolkit will be developed with feedback from the American College Health Association, which has agreed to partner with NIH on this initiative. NIH is also collaborating with the Health Resources and Services Administration (HRSA) to disseminate educational and training materials for providers and staff at HRSA-funded health centers through the *Women's Health Resources Web Portal*. For public education, ORWH also developed and distributed 60,000 copies of a publication entitled, *A Primer for Women's Health*, which contains a section on vulvodynia.

Research support from ORWH includes co-sponsorship of several Program Announcements (PAs) through NICHD for various research funding opportunities, including an announcement to encourage more R01 grant applications for vulvodynia research (<http://grants.nih.gov/grants/guide/pa-files/PAR-10-190.html>) as well as two related PAs for R21

and R03 funding opportunities. In addition, ORWH is a member of the NIH Working Group on Co-morbid Chronic Pain, which includes vulvodynia research.

Conference Significant Items

Item

Discretionary Fund. - The Office of the Director (OD) shall ensure, as practicable, the programs and offices within OD receive increases proportional to the overall increase, unless otherwise specified. (p. 30)

Action taken or to be taken

The table below shows the allocation of funding within the Office of the Director in FY 2011, FY 2012 enacted, and FY 2013 PB. NIH did not propose any major reallocations between activities in FY 2012 compared to FY 2011. Funding levels for the National Children’s Study and the Common Fund were specified in appropriations language in FY 2012.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Budget Mechanism - OD PPA

	FY 2011 Actual	FY 2012 Enacted	FY 2013 PB
OD Operations	\$ 122,837,000	\$ 123,203,000	\$ 123,081,000
NIH Director's Challenge Fund ¹	<i>1,500,000</i>	<i>1,500,000</i>	<i>1,500,000</i>
Division of Program Coordination, Planning and Strategic Initiatives	8,116,000	8,116,000	8,116,000
Office of Behavioral & Social Sciences Research	27,001,000	27,001,000	27,001,000
Office of AIDS Research	63,302,000	63,802,000	63,802,000
Office of Research on Women's Health	42,324,000	42,324,000	42,324,000
Office of Disease Prevention	6,065,000	6,065,000	6,065,000
Office of Dietary Supplements	27,717,000	27,717,000	27,717,000
Office of Research Infrastructure Programs	286,409,000	283,698,000	283,698,000
Science Education Partnership Awards	19,465,000	20,282,000	20,282,000
Office of Science Education	3,980,000	3,980,000	3,980,000
Director's Discretionary Fund	9,854,000	9,981,000	9,981,000
Foundation for the National Institutes of Health	493,000	493,000	493,000
Intramural Loan Repayment and Scholarship	7,393,000	7,393,000	7,393,000
Nuclear/Radiological/Chemical Countermeasures	95,298,000	95,298,000	95,298,000
National Children's Study	191,048,000	193,098,000	165,000,000
Common Fund	543,021,000	544,930,000	544,930,000
Total	\$ 1,454,323,000	\$ 1,457,381,000	\$ 1,429,161,000

¹/ Items in italics are "non-adds"; for reference only (NIH Director's Challenge Fund amounts are already included in OD Operations budget).

Item

Extramural Research. - In recent years, extramural research has accounted for nearly 90 percent of NIH's budget. The conferees strongly urge NIH to maintain at least that level in fiscal year 2012. NIH should also establish safeguards to ensure the percentage of funds used to support basic research across NIH is maintained. (p. 29)

Action taken or to be taken

In the past ten fiscal years, the proportion of the NIH budget spent on extramural programs has been steadily 83-84% and the proportion spent on intramural research had been 9-11%. Similarly, NIH has spent 52-55% of its budget on basic research in the past ten years, and 40-45% on applied research. The percentage in any given year has varied slightly due to scientific opportunities. NIH strives to achieve a balance between support for extramural researchers and a robust intramural program, as well as between basic research and applied research.

Fiscal Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012 Estimate
Extramural Research	83.7%	82.7%	84.2%	84.1%	83.6%	*84.2%	83.8%	83.6%	83.5%	82.9%	82.6%
Intramural Research	9.5%	9.4%	9.5%	9.6%	9.7%	*10.4%	10.4%	10.6%	10.7%	11.0%	11.0%
Basic Research	54.6%	51.9%	52.7%	55.0%	54.5%	53.7%	53.8%	51.6%	52.1%	51.9%	52.3%
Applied Research	39.4%	40.7%	43.3%	40.8%	42.0%	43.0%	42.2%	45.4%	45.0%	44.6%	45.2%
Total NIH Budget Authority (Millions)	\$23,559	\$27,173	\$28,036	\$28,644	\$28,516	\$29,128	\$29,607	\$30,546	\$31,234	\$30,917	\$30,852

*NIH's research program on Cancer Control and the budget of the National Library of Medicine were reported as separate line items in NIH's budget distribution reports up through FY 2006. In FY2007 these two items were reported for the first time in combination with NIH's extramural and intramural research, resulting in an apparent increase in extramural and intramural research spending.

Item

Lessons Learned. - Lessons learned with NCATS should guide NIH as it considers another proposed restructuring, one that would involve consolidating NIDA, NIAAA and components of other Institutes and Centers (ICs) into a new Institute devoted to research on substance use, abuse and addiction. The conferees understand that NIH plans to adopt a more deliberate approach in evaluating the need for this Institute. The conferees strongly recommend that this approach should include full consideration by the SMRB and that if the administration ultimately decides to seek such a restructuring, it should provide sufficient details in a formal budget request to Congress. (p. 31)

Action taken or to be taken

Please refer to page 151 of this document for the OD response to this significant item.

Item

New and Competing Research Project Grants [RPGs]. - NIH is strongly urged to ensure its policies continue to support a robust extramural community and make certain sufficient research resources are available to the more than 300,000 NIH-supported scientists at over 3,100 institutions across the country. The conferees affirm the critical importance of new and competing research project grants (RPGs) to the mission of NIH and are concerned that in the past few years, NIH has failed to support the number of new, competing RPGs that it estimated would be awarded in its annual congressional budget justifications. The conferees expect NIH to evaluate its new grant-estimating methodology to improve its accuracy and support as many scientifically meritorious new and competing RPGs as possible, at a reasonable award level, with the funding provided in this Act. (p. 29)

Action taken or to be taken

NIH appreciates the concerns expressed by the Committees regarding the accuracy of RPG grant-estimating methodology. Although in previous years noted variances were seen between projected counts and the actual numbers of new/competing RPGs, the projections and actual counts were much closer for FY 2011 under the continuing resolution (CR). The number of new/competing RPGs projected in the mechanism table update associated with FY 2011 full-year appropriations was 8,717. The actual number of new/competing RPGs in FY 2011 was 8,706. Both projected and actual RPGs are exclusive of 59 grants funded from the OD appropriation unrelated to the Common Fund. NIH will evaluate its RPG grant estimating methodology based on an assessment of how FY 2012 actual awards compare to projected numbers. As part of the review, FY 2012 results will also be compared to previous variances between RPG estimates and actual awards produced in FY 2011 and prior, years to refine identification of additional factors that may shape the number of awards.

Moving into FY 2012, NIH will continue to ensure that as many scientifically meritorious new/competing RPGS are funded as possible at reasonable award levels, in keeping with the proposed science as well as stated policy to avoid growth in the average competing RPGs.