

SIGNIFICANT ITEMS (SIs)

FY 2013 Senate Appropriations Committee Report
and
FY 2013 House Appropriations Committee Report

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National Cancer Institute (NCI)

Senate Significant Items

Item

Angiogenesis. - The Committee commends NCI for planning a scientific workshop to explore the effect of medication, diet, and lifestyle on angiogenic levels. The Committee encourages NIH to use this workshop to engage with the Trans-Institute Angiogenesis Research Program on implementing a vigorous agenda that examines current angiogenesis therapies in order to improve outcomes. The Committee also encourages NCI to examine angiogenic levels in the body prior, during, and after treatments. 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. 78)

Action taken or to be taken

Angiogenesis, or the formation of new blood vessels, plays an important role in cancer research. Tumors depend upon new blood vessels to supply oxygen and nutrients necessary for survival, growth, and spread. The National Cancer Institute (NCI) has long supported angiogenesis research and, over the past two decades, scientists have discovered a number of natural and synthetic agents that can block angiogenesis and thereby slow or stop tumor growth and spread.

NCI has a large clinical development program that is evaluating the therapeutic role of several antiangiogenic agents in cancer to explore strategies to optimize outcomes in patients. For example, NCI-sponsored Phase III clinical trials have evaluated the role of bevacizumab (a monoclonal antibody to target a major angiogenic factor called vascular endothelial growth factor (VEGF)) in breast, lung, colorectal, ovarian, pancreatic, prostate and cervical cancers. In many cases, the addition of bevacizumab led to an improvement in progression-free survival and, in some cases, improvement in overall survival. Results from NCI-sponsored bevacizumab trials have been used for FDA approval in colon and lung cancers. Additional bevacizumab Phase III trials are ongoing in patients with glioblastoma, bladder and head and neck cancers.

Major challenges in antiangiogenic therapies include the lack of predictive markers and the development of acquired resistance. Over the last few years, there has been an increasing emphasis on studies to identify predictive markers and mechanisms of resistance. Baseline blood and tumor tissues have been collected for retrospective analysis with the goal of identifying predictive markers for antiangiogenic therapy. Plasma VEGF levels have been recently identified as a promising lead and will be tested in samples from large randomized trials to validate its utility in identifying patients who are most likely to benefit from bevacizumab.

In an attempt to better understand the mechanisms of resistance, trials that incorporated intensive tumor biopsies and blood collections before and after treatment were developed and revealed that parallel angiogenic pathways may be responsible for resistance to anti-VEGF therapy. These findings have led to the need for further preclinical testing of combination strategies, of which NCI is currently sponsoring trials for a number of novel combinations.

In addition, dietary components with anti-angiogenic properties may be useful cancer prevention agents based on their ability to block transition of some pre-neoplastic lesions to certain types of cancer. Interestingly, both preclinical and human evidence suggest some bioactive food components may modify some early pathological angiogenic processes contributing to the development of cancer. These findings suggest dietary approaches focusing on angiogenic modification may be attractive targets for reducing cancer risk.

To further our knowledge in this area, NCI is in continuing discussions with other NIH Institutes and Centers (IC) to identify the gaps in the research portfolio on angiogenesis, including the role of diet and nutrition, and to identify and discuss research priorities. In addition, in May 2013, NCI, NIDDK, and NHLBI will be holding a workshop on angiogenesis and disease, focusing on cancer, diabetes, and heart disease.

Item

Breast Cancer. - The Committee remains concerned about the toll of triple negative breast cancer and urges NCI to collaborate with ORWH, NIMHD, OMH, and OWH to help improve treatment and survival rates. (p. 78)

Action taken or to be taken

Triple negative breast cancer (TNBC) lacks hormonal receptors for estrogen and progesterone, and the receptor HER-2 (human epidermal growth factor receptor 2). Therefore, therapies that target hormonal receptors (e.g., tamoxifen and aromatase inhibitors) or HER-2 (e.g., trastuzumab, lapatinib, and pertuzumab) are not effective in treating this disease, in contrast to tumors that are hormone receptor-positive or HER-2-positive. Chemotherapy can be effective in some women, but many women will suffer disease recurrence after initial therapy. Of the approximately 209,000 cases of breast cancer diagnosed in 2010, it is estimated that 15-20 percent (approximately 31,000-42,000 patients) were classified as TNBC. Groups at higher risk of TNBC include women under 50, African American and Hispanic women, and women of lower socioeconomic status. Regardless of the stage at diagnosis, women with TNBC have poorer survival than those with other breast cancers of the same stage. Among women with TNBC, the 5-year relative survival was 77 percent compared to 93 percent for women with other breast cancers. African American women with late-stage TNBC fared worst, with a 5-year relative survival of only 14 percent.

NCI and the National Institute on Minority Health and Health Disparities (NIMHD) are studying linkages between race, obesity, TNBC, and biomarkers of drug resistance in breast cancer cells. NCI also collaborates with the Office of Research on Women's Health (ORWH) on projects that integrate tumor models and imaging to predict response in TNBC. NCI and ORWH are also evaluating breast cancer subtypes, ancestry, and the relationship between specific risk factors and breast cancer subtype in Hispanic Women.

While TNBC is heterogeneous (not all patients will have the same type of cell abnormalities), about 80-90 percent of TNBC falls into a subcategory called "basal-like breast cancer." In 2011, NCI-funded researchers identified six distinct TNBC subtypes, each with specific molecular

candidate targets, and developed cell lines for each tumor subtype. These findings may provide biomarkers that can be used for patient selection in the design of clinical trials, as well as a way to measure response to treatment. This study, together with others, has identified several potential targets that may be amenable to treatment.

Recently, more extensive genomic data from The Cancer Genome Atlas (TCGA), published in *Nature* magazine on October 4th, revealed a series of similarities in the types and frequencies of genomic mutations between basal-like breast cancer (TNBC) and serous ovarian cancer. Analyses show that both types might be susceptible to agents that inhibit the growth of blood vessels and cut off the blood supply to the tumor, as well as chemotherapy drugs (such as platinum agents) and new agents such as poly ADP ribose polymerase (PARP) inhibitors that selectively kill cancer cells with defective DNA repair mechanisms (a type of cancer cell present in TNBC). Understanding the similarities between these cancer types will provide researchers with the opportunity to compare treatments and outcomes of both cancers.

Ongoing clinical trials are examining the role of anti-angiogenesis agents, platinum compounds, PARP inhibitors, and other targeted agents in TNBC, in addition to molecular profiling to help determine which sub-types of TNBC will respond to the different therapies. For example, NCI is supporting a pre-operative study to see if adding other drugs to standard neoadjuvant chemotherapy can help shrink TNBC faster and lower the risk of the cancer coming back in other parts of the body. This study is specifically working to encourage accrual from African American women. The study will also collect tumor tissue to learn more about potential targets for therapy in TNBC. Additionally, NCI intramural researchers identified two genes (CHK1 and RRM1/2) that are intimately related to the growth of TNBC cells in a synergistic manner. Based upon these results, NCI is developing a clinical trial to treat these patients with drugs that target these genes. As research efforts continue to identify and validate additional candidate targets, those that have inhibitors will be studied in future clinical trials, while others provide an opportunity for inhibitor development.

Preventing TNBC will continue to be a critical goal for NCI. Obesity has been associated with a greater risk of mortality from breast cancer, including TNBC, and some studies also link inflammation to increased risk. NCI is therefore conducting studies to explore whether reversing obesity and inflammation may lower the risk of developing, or dying from, breast cancer. These include life-style interventions (weight-control, exercise), as well as studies to explore the role of anti-inflammatory agents.

Item

Cancer Disparities. - The Committee urges NCI to fund basic, translational, and clinical research on cancer disparities in regions of the country that have a high predominance of economically disadvantaged African Americans. Specifically, the Committee urges further research on novel immune therapeutics intervention in cancer areas relevant to human papilloma virus and genomics etiologies in cancer areas relevant to smoking and obesity. (p. 78)

Action taken or to be taken

NCI's research portfolio includes a broad range of studies that stimulate and support basic, translational, and community-based population research on the biological and non-biological determinants of cancer health disparities among racially and ethnically diverse populations. Current projects focusing on African Americans include examining genetic and epigenetic factors for prostate cancer disparities, identifying molecular signaling pathways in breast cancer, and identifying genetic variations for colorectal cancer disparities. Recent evidence from an NCI study suggests that certain genetic alterations of a protein that inhibits inflammation are associated with increased susceptibility to colon cancer in African Americans.

NCI's programs on cancer disparities include the national and regional Community Networks Program (CNP) Centers and the National Outreach Network, which conduct community-based research projects in areas with a higher predominance of economically disadvantaged African Americans. These projects are aimed at improving education, outreach, and training activities to reduce cancer disparities by increasing readiness to participate in biospecimen research and clinical trials, as well as healthy lifestyle behaviors such as cancer screenings, human papilloma virus (HPV) screening and vaccination, smoking cessation, diet and exercise, and better communication with healthcare providers. Research is under way to promote HPV screening and test the efficacy of a home-based self-administered test among African American communities.

NCI is continuing a 10-year follow up of an HPV vaccine trial in Costa Rica that enrolled approximately 7,500 women to assess the immunologic changes in participants over time related to duration of protection and long-term effects of HPV vaccination. In addition, NCI is supporting research on the role of HPV in head and neck cancers, which, along with other HPV-related cancers, are common in underserved populations. The studies will optimize treatment of patients with HPV-associated head and neck cancers to improve disease control and survival and minimize toxicity.

NCI's Geographic Management of Cancer Health Disparities Program (GMaP) focuses on connecting at-risk and underrepresented communities with NCI research, training, and outreach efforts to advance our understanding of cancer health disparities. GMaP has three networks focused on cancer disparities infrastructure development and research in regions with a high proportion of economically disadvantaged African Americans. A regional GMaP multisite obesity reduction project is being conducted among low-income rural and urban African Americans to identify and assess inflammatory biomarkers as part of a culturally tailored weight loss intervention. The Biospecimen/Biobanking Geographic Management Program (BMaP), a specialization within GMaP, includes a pilot to build regional African American and Hispanic breast cancer biobanking capacity. BMaP is working to end disparities in biobanking and to enhance understanding of biological and genomic influences in cancer disparities.

As part of the Provocative Questions (PQ) Project, NCI hosted a meeting on October 26, 2012 in San Diego, California to develop health disparities-specific provocative questions in the areas of tumor development, recurrence and detection, diagnosis, and prognosis. Discussions from this meeting, which included health disparities experts as well as researcher from other fields, will be used to help guide the future of the PQ Project, which aims to engage a diverse range of

scientists in a challenging intellectual exercise to define then solve the major unsolved or neglected problems in oncology.

Item

Liver Cancer. - The Committee recognizes NCI's efforts in the area of liver cancer, but encourages a stronger effort to include funding of a specialized program of research excellence on this disease as well as liver cancer program projects focusing on pathogenesis, detection, and/or therapeutics. (p. 78-79)

Action taken or to be taken

NCI continues to leverage its resources to develop new detection, intervention and treatment approaches for hepatocellular carcinoma (HCC), and to encourage applications for Liver Cancer/HCC and/or Gastrointestinal Specialized Programs of Research Excellence (SPOREs) that include an emphasis on HCC. Currently, NCI staff anticipate that several institutions will be submitting Liver Cancer SPORE applications in 2013. NCI continues to support various HCC research efforts through its intramural and extramural portfolios.

Through the SPOREs program, NCI is supporting research at the University of Kentucky GI SPORE on the hepatitis C virus (HCV) in an attempt to understand the relationship of HCV protein expression and cell proliferation to provide preventive, diagnostic, and therapeutic opportunities for liver cancer. It is also trying to determine whether HCV infection alters the expression of tumor suppressor proteins in hepatocyte liver cells. Other GI SPORE research includes an analysis of HCC stem cells and micro-environmental influences on immune cells.

NCI supports clinical trials on therapeutics for liver cancer, including a recent Phase III trial of advanced diagnostic imaging techniques; a Phase II clinical trial of cabozantinib in HCC; and a Phase II study of proton beam therapy to kill cancer cells in the liver, allowing for more precise treatment and reduced toxicity. The multi-institutional trial involves the Massachusetts General Hospital, the Dana-Farber Cancer Institute, and the MD Anderson Cancer Center.

Genomic analysis of HCC is increasing our understanding of this disease. For example, in 2012, investigators in NCI's intramural program identified a 10-gene signature linked to HCC with poor prognosis and later validated these findings in analyses of five independent cohorts. The team also identified cancer "driver" genes in HCC with poor prognosis and validated three new tumor suppressor genes in HCC.

In another study, researchers determined that cholangiocarcinoma (CCA), a rare type of liver cancer, is actually composed of four subgroups. They found that the CCA subgroup with the worst prognosis had a distinct genomic profile that is characterized by mutations of the KRAS gene, as well as increased expression of cell surface receptors HER2 and EGFR. These findings offered a possible explanation as to why some treatments were ineffective for these patients. To test this possibility, NCI researchers treated CCA cell lines with the drug lapatinib, chosen because of its ability to inhibit both EGFR and HER2. They found lapatinib was significantly more effective at inhibiting cancer cell growth for this subtype of CCA than another drug (trastuzumab) that targets HER2 only.

Intrahepatic cholangiocellular carcinoma (ICC) is the second most common type of primary liver cancer. NCI investigators found that specific ICC gene signatures could predict survival, and that a common signaling pathway was preferentially activated in ICC with stem cell gene expression traits. NCI investigators are also studying liver cancer risk factors, including human genetic factors that affect response to treatment for chronic infection with HCV. Major advances in the treatment of chronic HCV infection include the use of direct-acting antiviral (DAA) agents that have led to the substantial improvement in responses. Researchers have found that aspirin use is associated with reduced risk of developing HCC and of dying of chronic liver disease. Another NCI effort is identifying medications that may affect HCC risk, and researchers are also evaluating medications that may be related to a decreased risk of HCC, such as diabetes drugs, statins, bisphosphonates, and others.

A Trans-NIH Committee on Viral Hepatitis, led by NIDDK, was formed to help develop a plan on behalf of NIH for implementing assigned goals in the U.S. Department of Health and Human Services' "Action Plan for the Prevention, Care & Treatment of Viral Hepatitis." In 2012, SBIR and STTR program announcements were released, calling for applications for the development of new technologies for the diagnosis, monitoring, management, treatment and prevention of viral hepatitis and viral hepatitis associated liver disease. Thus far, NCI has received 40 applications for these program announcements. NCI is the primary Institute on eight of them and secondary on the remaining 32. Of the eight at NCI, funding decisions have yet to be made, but will be completed by September as all of the applications received are for FY 2013. Of the 32 that NCI is secondary on, two have already been awarded by the National Institute for Allergy and Infectious Diseases.

Item

Lung Cancer. - The Committee commends NCI for its National Lung Screening Trial and urges the Institute and partner agencies to move forward in translating these findings into public health recommendations. The Committee requests an update in the fiscal year 2014 congressional budget justification about the benefits of screening among high-risk groups including women, African-American men, and those with other co-morbidities. (p. 79)

Action taken or to be taken

On June 29, 2011, the primary results of the National Lung Screening Trial (NLST) were published online in the *New England Journal of Medicine* and revealed that participants who received low-dose helical (spiral) computed tomography (CT) scans had a 20 percent lower relative risk of dying from lung cancer than participants who received standard chest X-rays. Launched in 2002, NLST compared these two ways of detecting lung cancer to find their effects on lung cancer death rates in a high-risk population of current or former heavy smokers ages 55 to 74.

In the NLST, 41 percent of subjects were women and 4.4 percent were African Americans. A substantial number of all participants had co-morbidities: 17.4 percent had chronic bronchitis, emphysema or chronic obstructive pulmonary disease (COPD); 9.7 percent had diabetes; 12.7 percent had heart disease or history of myocardial infarctions; and 35.4 percent had

hypertension. Analyses of NLST data are ongoing as to the effect of CT screening in these various sub-groups of gender, race, and co-morbidity status. NCI is also conducting risk projection work to estimate the potential radiation-related cancer risks for the types of patients in NLST (similar smoking history, age, etc., and with the same screening history of three spiral CT screens). These potential risks from radiation from the screening procedure will be compared with the benefits observed in the trial. Datasets and digital screening images from the NLST are being made available for use by other researchers via an Internet portal. This information was made public beginning in October 2012.

Additional studies based on the complete NLST dataset will help guide decision making, including an analysis by NCI's Cancer Intervention and Surveillance Modeling Network (CISNET), which is currently examining cost effectiveness of CT screening compared to the cost effectiveness of smoking cessation. CISNET models help examine how tobacco control interventions, treatments, and public policies may affect lung cancer incidence and mortality. CISNET studies have also been commissioned by the United States Preventive Services Taskforce (USPSTF) to fully assess the risks and benefits of lung screening with low-dose helical CT. These models will be used to estimate the benefits and harms of screening under a variety of scenarios. Over the next year, the USPSTF is convening a panel to provide recommendations about lung cancer screening.

Regardless of screening decisions, avoiding tobacco is the most powerful way to lower individual risk of death and suffering from lung cancer. Given the important role and efficacy of evidence-based population and clinical smoking cessation interventions in reducing lung cancer mortality, it is important that screening programs complement, not compete with, smoking cessation efforts and programs. Depending on how screening is implemented, it is possible that widespread screening could either increase or decrease attempts to quit (i.e., if smokers perceive that a negative screening means they don't need to quit). NCI seeks to learn more through a secondary analysis of the cessation behavior of participants in the NLST (control and screening arms), which is expected in the next year.

NCI and the Centers for Disease Control and Prevention (CDC) are currently discussing ways to work together to determine the impact of implementation of lung cancer screening by low-dose helical CT scan on patterns of smoking cessation and initiation. NCI and CDC are also seeking ways to increase smoking cessation rates in conjunction with helical CT screening for lung cancer.

Item

Melanoma. - The Committee continues to encourage NCI to support research directed at the biology of tumor initiation including UV radiation as a carcinogen, the immunologic and addictive effects of UV radiation, host risk factors, and risk reduction strategies. Research into the relative utility of novel early detection strategies is encouraged, including leveraging recent advances in imaging technology. Despite two recent drug approvals for advanced melanoma, cures are rare. Research strategies with curative potential that build on these advances should be supported, including examining mechanisms of drug resistance to molecularly targeted therapies such as BRAF gene inhibitors. The Committee also urges more research on treatment strategies

for the 50 percent of patients without BRAF mutations, as well as on predictive biomarkers that correlate with immune response to ipilimumab. Finally, the Committee urges NCI to promote collaborations between industry, the extramural program, and foundations that will accelerate translational and clinical research. (p. 79)

Action taken or to be taken

NCI continues to investigate associations between ultraviolet (UV) radiation and the development of skin malignancies. Recently published data identify two distinct pathways for melanoma development, providing new insights into the relationships between melanoma and UV radiation in sunlight and expanding possibilities for novel therapeutic approaches. NCI is leading national and international collaborations for the molecular characterization of melanoma tumors. In high-risk families, NCI researchers are employing new technology to identify melanoma susceptibility genes. To further prevention and detection methods, NCI led development of the Melanoma Risk Assessment Tool (MRAT) to assess the risk of developing melanoma over a five-year period. Healthcare providers can use the tool (available at www.cancer.gov/melanomarisktool) to identify high-risk patients and employ interventions to decrease risk or to enhance early detection. NCI is also supporting research to better understand motivation for tanning and to inform development of innovative interventions to change behaviors related to tanning.

Until recently, people with advanced melanoma had little chance of survival beyond a few months, but new drug approvals have provided some hope. Ipilimumab, approved by the FDA in 2011, is among the first of a new and growing family of drugs designed to attack cancer using a patient's own immune system. Data published in April 2012 showed that ipilimumab can induce durable, potentially curative tumor regression in a small percentage of patients with metastatic melanoma. Key research leading to the approval of ipilimumab was made possible by sustained NCI funding for over a decade.

Also receiving FDA approval in 2011 was vemurafenib, a drug for patients with metastatic or inoperable melanoma whose tumors have a gene mutation called BRAF V600E. The BRAF V600E mutation is present in about half of patients with metastatic melanoma. Typically, patients have dramatic initial responses to treatment with selective BRAF inhibitors, but then drug resistance emerges and tumor suppression is lost. NCI is supporting research on the mechanisms underlying drug resistance, including preclinical studies and clinical trials investigating whether the risk of resistance can be reduced by strategic combination chemotherapy. Other research includes comprehensive genome characterizations to better understand the 25 percent of melanomas that do not have known BRAF mutations. Recently published data has identified six novel melanoma genes, including three that harbor recurrent "hot-spot" mutations that are potential drug targets.

As an example of collaboration between NCI and industry partners, NCI's Surgery Branch has developed new and highly effective treatments for melanoma based on the administration of autologous lymphocytes (white blood cells) with anti-tumor activity. A new biotech start-up company licensed this work and is attempting to commercialize it to make it more widely available. NCI has also built networks of investigators to explore drug resistance and to develop

better preclinical models for recurrent metastatic disease, bringing together teams from NCI, extramural and international investigators, and pharmaceutical companies.

Over the past year, NCI has convened two meetings to discuss collaborative opportunities with several melanoma research advocacy organizations, and this effort is ongoing. NCI also participated in a stakeholders meeting, convened by the Department of Health and Human Services, Office of the Assistant Secretary for Health, in September 2012, to discuss melanoma screening and prevention research findings.

Item

Neuroblastoma. - The Committee encourages NCI to expand its research portfolio on this deadly pediatric cancer, including the development of new treatment options for children suffering from central nervous system [CNS] relapses. The Committee requests an update on this research, including the potential utilization of chimeric antibody immunotherapy for CNS-relapsed neuroblastoma, in the fiscal year 2014 congressional budget justification. (p. 79)

Action taken or to be taken

NCI is working to address and improve outcomes for children with neuroblastoma, beginning with understanding the biology of neuroblastoma and translating this to more effective treatments for patients. Multiple research projects are supported by NCI to improve outcome for children with newly diagnosed and relapsed neuroblastoma. Several examples include:

- The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative: a project to identify and validate new therapeutic targets through the application of large-scale state-of-the-art genomics methods is studying high-risk neuroblastoma.
- Pediatric Preclinical Testing Program (PPTP): an initiative that has tested more than 50 agents against neuroblastoma preclinical models in the past 5 years.
- The New Approaches to Neuroblastoma Therapy (NANT) Consortium: an NCI-supported consortium evaluating complex and new treatment strategies for children with neuroblastoma.
- The Children's Oncology Group (COG): an NCI-supported clinical trials cooperative group devoted exclusively to childhood and adolescent cancer research.
- The COG Phase 1 / Pilot Consortium: a small consortium dedicated to safely introducing novel agents as childhood cancer therapeutics, with many studies focused on neuroblastoma. Recent findings include a trial featured at the June 2012 American Society of Clinical Oncology (ASCO) meeting showing promising results using crizotinib to treat pediatric patients with anaplastic large cell lymphoma and neuroblastoma.

Experts are working to revise the international neuroblastoma response criteria to facilitate global scientific collaborations. In April 2012, NCI convened an international consensus meeting on response criteria in Washington, D.C. In follow-up to this meeting, North American and European research teams drafted manuscripts summarizing the entire meeting as well as specific topics discussed at the meeting; including neuroblastoma Phase II clinical trial design, interpretation of metastatic imaging, and bone marrow response criteria. An additional manuscript, focusing on response criteria for primary sites, is in the data analysis phase. Leaders of the effort are exploring the most appropriate venue for publishing the manuscripts. The

revised response criteria are being developed from the meeting presentations and discussions from the post-meeting activities will have a significant impact on future neuroblastoma trials for patients with relapsed/refractory disease.

NCI continues to develop the immunotherapy of the Ch14.18 antibody (a chimeric mouse/human monoclonal antibody with potential to prevent or inhibit the maturation, growth, or spread of tumor cells) with the COG and NANT. NCI has driven more than 20 years of intramural and extramural research on antibody-based immunotherapy to bring this new life-saving treatment to children with aggressive neuroblastoma. NCI has supported the entire spectrum of development of Ch14.18, from discovery to the Phase III COG study that proved the substantial therapeutic advance represented by this treatment, and even producing the agent itself when no pharmaceutical company was willing to manufacturer it for the Phase III trial. NCI is also supporting two new Ch14.18 trials that will include patients with a history of CNS-relapsed neuroblastoma.

In collaboration with extramural colleagues and the private sector, NCI's Pediatric Oncology Branch has initiated an individualized cancer therapy trial for high-risk neuroblastoma patients, utilizing genomic profiling of patient tumors to develop a personalized treatment regimen for high-risk pediatric cancer. NCI scientists have also discovered a new tumor suppressor gene (CASZ1), which serves as a "master switch" that regulates an array of oncogenes in neuroblastoma. Researchers have also identified an important role for the AKT pathway (a pathway involved in cellular survival and implicated in many types of cancer) and demonstrated antitumor effects of an AKT inhibitor in mouse models of this disease.

Item

Pancreatic Cancer. - While survival rates for many types of cancer have steadily improved, the rate for pancreatic cancer has remained in the single digits for over 40 years. With the number of new cases of pancreatic cancer projected to increase 55 percent between 2010 and 2030, the Committee urges NCI to create a comprehensive, long-term research strategy for this disease that focuses on increasing survival. The plan should not be simply a summary of recent and ongoing research activities. Rather, it should set out concrete goals for the future. The Committee requests an update in the fiscal year 2014 congressional budget justification on the steps NCI is taking to create such a plan.

Action taken or to be taken

It is estimated that there will be nearly 44,000 new diagnoses of pancreatic cancer in the United States in 2012 and about 40,000 deaths; furthermore, the incidence is expected to increase in coming years due to the aging of the population. Well over 90 percent of pancreatic malignancies are classified as pancreatic ductal adenocarcinomas (PDAC), tumors that arise in the ducts that carry pancreatic digestive enzymes to the small intestine. Known risk factors for PDAC include tobacco use, diabetes, inflammation of the pancreas, obesity, and a family history of pancreatic cancer.

Despite substantial increases in NCI's funding of research on PDAC and in the number of investigators working on this disease over the past decade, it has proven difficult to improve

clinical outcomes, especially the high mortality rate and poor five-year survival. The obstacles to progress include the cancer's complex biology, the lack of early screening tools, the typical lack of symptoms until the tumor is relatively far advanced, and the inability to induce durable responses to existing chemotherapeutic agents in most patients. One of the major factors limiting the effectiveness of systemic therapies is the characteristic presence of dense layers of fibrotic (scar) tissue surrounding PDACs, which limits the penetration of drugs into the tumor.

Nevertheless, considerable strides have been made in understanding the pathogenesis of this disease through the development of animal models that mimic key aspects of PDAC, detailed analyses of primary and metastatic human PDAC, characterization of PDAC cell lines, identification of genetic and epigenetic changes that are needed for normal pancreatic cells to undergo malignant transformation, and inherited mutations that predispose to the disease. Even more comprehensive analyses of the genomic changes in PDAC are currently under way through The Cancer Genome Atlas (TCGA), a joint research initiative of NCI and the National Human Genome Research Institute (NHGRI).

Studies of human PDAC have found that each pancreatic cancer contains multiple mutations in various genes. While many of the affected genes differ between individuals with PDAC, well over 90 percent of PDACs have a mutated KRAS gene, which is a major genetic driver of pancreatic cancer initiation and progression. This same mutant gene is also found in some aggressive lung and colon cancers. NCI-supported studies of mouse models and pancreatic cancer cell lines suggest that inhibiting KRAS is critical to obtaining a durable response. However, despite decades of research on KRAS in the public and private sectors, the development of clinically successful KRAS inhibitors, for any tumor type, has thus far proven elusive. The central role of KRAS in PDAC probably makes an important contribution to the relative resistance of PDAC to a wide variety of therapies that do not target KRAS.

NCI is taking additional steps to attempt to improve patient outcomes with PDAC. These include defining important, unsolved problems in PDAC research and identifying methods to solve these problems. To explore such scientific opportunities, Harold Varmus, Director of the National Cancer Institute, convened a meeting October 23 and 24, 2012, of experts in the areas of gastrointestinal, medical, surgical, and radiation oncology, basic and translational research, and patient advocacy to evaluate possible new areas of PDAC investigation. NCI asked this Working Group (which reports to the NCI's Clinical Trials and Translational Research Advisory Committee) to identify key research questions in epidemiology and risk assessment, pathology, screening, early detection, and therapeutics and to recommend new and expanded approaches to solve important aspects of PDAC.

Based on this meeting and other recent PDAC conferences, NCI is currently developing more specific plans for its portfolio of research on PDAC. These will likely include continuing efforts to understand the genetic underpinning of pancreatic cancer (through the activities of the TCGA consortium and others); the development of cohorts of individuals at high risk of developing pancreatic cancer based on their family histories, the high incidence of PDAC in patients recently diagnosed with diabetes mellitus, environmental risk factors, or the presence of pre-malignant cystic or non-cystic pre-invasive lesions of the pancreas; improvements in methods of early detection; the expanded use of genetically-engineered mouse models of PDAC and patient-

derived tumor implants in mice to more effectively evaluate new therapeutic agents before they come to the clinic; the use of these models to discover biomarkers of early stage disease; the support of novel immunotherapeutic approaches that have recently shown substantial promise in the treatment of other cancers; and a concerted attempt to develop therapeutic agents (both drugs and immunotherapeutics) against the mutated KRAS gene that is a major driver of tumor proliferation in PDAC.

NCI will continue to support the existing, large portfolio of research project grants on PDAC, with its balance of basic, translational, and clinical studies that address the characteristics of PDAC cells and the tumor microenvironment; the roles of heredity and inflammation in the etiology of PDAC; and several approaches to the prevent, screening, diagnosis, and therapy of PDAC. Studies of a number of topics not specifically categorized as PDAC research – for example, basic studies of KRAS and the role of KRAS mutations in other types of tumors—are also critical for progress against PDAC.

NCI has conducted several prior assessments of ongoing research and scientific opportunities for pancreatic cancer in recent years. In 2008, for example, the NCI Gastrointestinal Steering Committee, which is composed of leading cancer experts who provide advice to NCI's clinical trials program, convened a group to discuss the integration of basic and clinical knowledge in the design of clinical trials for PDAC. The group published a Consensus Report in the *Journal of Clinical Oncology* (<http://jco.ascopubs.org/content/27/33/5660.full.pdf>). In 2012, representatives of NCI also participated in a large meeting about the progress and challenges in pancreatic cancer hosted by the American Association of Cancer Researchers (AACR).

Additionally, NCI has convened a Pancreatic Cancer Working Group of the NCI Clinical and Translational Research Advisory Committee (CTAC). The working group is developing a research framework and report to Congress consistent with the requirements of the Recalcitrant Cancer Research Act.

Item

Pediatric Cancer. - The Committee continues to urge NCI to devote more of its funding specifically for research on pediatric cancer, including pediatric low-grade astrocytoma. The Committee requests an update in the fiscal year 2014 congressional budget justification, including efforts that could result in more effective, less toxic treatments.

Action taken or to be taken

NCI supports a comprehensive research program for children with cancer, including basic molecular projects, preclinical testing and clinical trials, and epidemiological studies. In fiscal year 2012, NCI invested \$209.4 million in pediatric cancer research, which includes funding for pediatric low-grade astrocytoma, and approximately \$1.97 billion in critical basic research exploring cancer biology and cancer causation, a type of research that contributes heavily to the understanding of all cancers, including those that affect children.

The NCI portfolio includes a number of programs designed to coordinate, advance, and sustain efforts in pediatric cancer research. NCI's Therapeutically Applicable Research to Generate

Effective Treatments (TARGET) initiative is a project to identify and validate new therapeutic targets for pediatric cancers through the application of genomics analyses. TARGET also supports the development of more effective, less toxic therapies. To date, the initiative has led to two clinical trials for new drugs against childhood tumors and identified numerous new mutations and chromosomal abnormalities associated with pediatric tumors.

Other efforts include the Pediatric Preclinical Testing Program (PPTP), which develops preclinical models representing a wide range of childhood cancers. PPTP has tested more than 50 agents in the past five years, with several PPTP-tested agents moving into clinical testing. The Pediatric Brain Tumor Consortium (PBTC) conducts early phase clinical trials for experimental therapies for children with brain cancers. NCI also funds significant research efforts through the Children's Oncology Group (COG), a cooperative that develops and coordinates pediatric cancer clinical trials at over 200 leading institutions. COG includes a consortium dedicated to safely introducing novel agents. COG also manages international studies, allowing for more pediatric cancer patients to be enrolled into clinical trials. Compared with adult cancers, a much higher percentage of children with cancer are enrolled in clinical trials. Together, these features help trials reach their clinical endpoints sooner, thus demonstrating more quickly whether a new treatment is better than the current standard of care. NCI also supports the multi-institutional Childhood Cancer Survivor Study (CCSS) to learn more about the late effects of childhood cancer treatment.

In the NCI's intramural program, the Pediatric Oncology Branch (POB) within the Center for Cancer Research (CCR) engages in research that spans basic, translational, and clinical trials focused on drug development of targeted agents, genomics, immunotherapy, and imaging research. NCI's Division of Cancer Epidemiology and Genetics (DCEG) conduct studies to understand the causes and risk factors for cancers in children. NCI investigators are also collaborating with extramural investigators to study subsequent cancers and late toxicity of treatment in survivors of childhood cancer. These efforts include leading a genome-wide association study to identify genetic variants that predispose childhood cancer survivors to the development of cancers later in life.

A study published in 2012 also addresses the development of secondary cancers. The study examines the increased risks of leukemia and brain tumors among children exposed to diagnostic radiation from CT scans, which could lead to a reduction in the frequency of CT scans. Such a reduction should lead to fewer malignancies resulting from this diagnostic procedure.

Another highlight of current research includes a study to determine whether genetic variation in the PDE4B gene may help explain differences seen in acute lymphoblastic leukemia (ALL) outcomes by race; significantly higher relapse rates are seen in Blacks and Hispanics. Additional efforts include two highly innovative studies of cell based immunotherapy for childhood cancer and research seeking to facilitate reducing distress and improving long-term quality of life for survivors and their families.

Item

Robotic Biorepository Technology. - In order to determine the genetic differences in the development, progression, and response to treatment of individuals with cancer, biospecimens (e.g. blood, urine, tumor tissue) must be collected and evaluated. Under some circumstances, high throughput, robotic instruments for the processing and storage of biospecimens can improve the efficiency and consistency of handling and distribution of these samples. In an effort to adequately address the increasing demand for these specimens, an automated approach should be considered when appropriate. Robotic biorepositories may also allow researchers to expand the collection of tissue specimens. A related goal is to ensure an adequate supply of high-quality human biospecimens from multiethnic communities for research to understand and overcome cancer health disparities. The Committee encourages NCI to explore the applicability of robotic biospecimen collection technologies and the establishment of regional robotic biorepositories in an effort to advance cancer research. (p. 80)

Action taken or to be taken

NCI funds and manages large biological specimen collections comprised of tissue, blood, urine and other solid and liquid samples. These specimens are processed and stored in freezers or in other appropriate conditions in NCI biorepositories. Automation and robotics have been used for many years in biorepositories, generally through the use of bar codes, which greatly reduce errors in specimen inventory systems; and instruments that quickly divide large numbers of liquid samples into smaller portions or “aliquots.” Automated freezers that can store and retrieve samples (tissue or liquid) that are processed into standard size storage vials are also commercially available. Under the right circumstances, automation and robotics are viable solutions to increase the efficiency and accuracy of biological sample processing. However, for robotics to be considered for widespread use at NCI biorepositories, it will be necessary to consider the function of the biorepository, the types and numbers of specimens to be collected, and ways to ensure that they are processed and stored in standardized containers amenable to automation. In addition, the technology is still emerging, and further testing by manufacturers is necessary to ensure that the robotics are reliable at the cold temperatures necessary to handle valuable biospecimens.

NCI’s Cooperative Human Tissue Network (CHTN) collects and ships samples to investigators with minimal processing and storing of tissues, and so does not currently have a need for robotic technology. In contrast, the NCI Cooperative Group Banks often handle large numbers of samples and so could benefit from robotics such as high-capacity instruments to locate and select test tubes and load and store new inventory from racks while unattended. And due to the large numbers of biospecimens that are used for population-based studies, automated technologies have improved NCI’s ability to access specimens.

To help ensure an adequate supply of high-quality biospecimens from multiethnic communities, the NCI Center to Reduce Cancer Health Disparities (CRCHD)’s Geographical Management of Cancer Health Disparities Program (GMaP) includes a specialization in Biospecimen Science (G/BMaP). G/BMaP is creating five regional hubs of connectivity for the support and efficient management of cancer health disparities research, training and infrastructure. Each region includes a specialization in biospecimen science. Key projects include a collaborative, multi-institutional pilot focused on building regional African American and Hispanic breast cancer

biobanking capacity. Eleven partnering institutions in Louisiana, Michigan, Alabama, Georgia, Florida and Puerto Rico are working to enhance our understanding of biological and genomic influences in cancer disparities. Another 19-institution regional partnership is focused on ending disparities in racial/ethnic biobanking. It includes the development of a culturally tailored, evidence-based biospecimen education module for dissemination among six racial/ethnic populations. This project has also led to a collaborative contract for racial/ethnic specimen collection through The Cancer Genome Atlas (TCGA).

Item

Shared Medical Decisionmaking. - The Committee encourages NCI's collaboration with OBSSR to study shared medical decisionmaking and to identify ways to improve communications between healthcare providers and their patients. (p. 80)

Action taken or to be taken

To explore the current evidence base for Shared Medical Decision Making (SMDM) and to identify promising lines of inquiry for future research, the OBSSR, in partnership with NCI and other NIH ICs, convened a 1-day workshop in May 2012. The Workshop resulted in suggestions for several potential funding opportunities.

NCI has sponsored several projects as part of its emphasis on facilitating the delivery of patient-centered cancer care. In 2007, NCI published the landmark monograph, *Patient-Centered Communication in Cancer Care: Promoting Healing and Reducing Suffering* that identified six core communication functions, including facilitating shared medical decision making, which health care organizations need to optimize as part of delivering high-quality cancer care. From 2007-2010, NCI collaborated with the Agency for Healthcare Research and Quality (AHRQ) to facilitate the systematic measurement of patient-clinician communication, resulting in a comprehensive set of survey items that are available to researchers to evaluate cancer patients' perceptions of the quality of communication with their clinicians. Since 2009, NCI has also been collaborating with AHRQ on an ongoing project to develop and test a cancer version of the Consumer Assessment of Healthcare Providers and Systems survey (CAHPS), considered the national gold standard for measuring quality of care from the patient's perspective. Since 2008, NCI has collaborated with Memorial Sloan-Kettering Cancer Center to develop and test an electronic patient-reported system for monitoring and reporting adverse symptoms that cancer patients may experience during treatment. It aims to facilitate communication and decision-making between cancer patients and clinicians to minimize patient suffering from adverse events. Beginning September 2012, NCI is also funding a 5-year grant to the University of Michigan to evaluate multiple factors likely to influence the treatment decision-making process for women diagnosed with early-stage breast cancer who are at risk for receiving aggressive treatments. The project will develop and evaluate educational tools for both physicians and patients to facilitate shared treatment decision making.

Patient communication has also been one of the research themes of the NCI-funded HMO Cancer Research Network (CRN). Research includes the development and assessment of new instruments that make it possible to conduct objective research on whether patients understand written or oral communication. These and other tools have been applied to examine health

system, physician, and patient communication dynamics surrounding adverse events during the course of cancer treatment. The Centers of Excellence in Cancer Communication Research is another key NCI funding initiative that supports research and outreach aimed at increasing the knowledge about, tools for, access to, and use of cancer communications by the public, patients, survivors, and health professionals. Several projects under this initiative have a decision-making component. Additionally, NCI has provided funding opportunities that have generated numerous grants to develop and test decision aids that educate patients so that they can engage in informed, shared decision making with their health care provider.

Item

Tumor Lysis Syndrome [TLS]. - The Committee understands that identifying high-risk patients, taking preventive measures, and closely monitoring patients are all key in fighting TLS, a lifethreatening oncologic emergency that is frequently encountered during and/or after the treatment of a variety of cancers. The Committee encourages NCI to convene an expert panel or working group to evaluate current risk assessment models, recommend a standardized assessment tool, and develop a plan of action to validate and disseminate the tools in clinical practice. (p. 80)

Action taken or to be taken

Tumor Lysis Syndrome (TLS) is a serious clinical challenge in the treatment of children and adults with certain leukemias, lymphomas, and some solid tumors. In recognition of this, the NCI-sponsored Physicians Data Query (PDQ) describes the importance of addressing TLS and outlines an approach to its treatment with appropriate citations to the published literature.

With the availability of newer therapeutic targeted agents for TLS, such as recombinant urate oxidase (rasburicase), an international expert panel was convened in 2008 and issued a report in 2010. These experts were comprised of both adult and pediatric oncology experts, representing diverse tumor specialization, and included a number of oncologists representing NCI-designated cancer centers. They proposed a classification that distinguishes laboratory TLS (LTLS) from clinical TLS (CTLS). It is a simple and easy to use clinical tool that provides a basis for recent TLS management guidelines as well as future TLS studies. The clinical tool is based on 40 years of data on incidence, prophylaxis, and treatment of TLS.

The panel made firm recommendations for monitoring LTLS on the basis of three clinical scenarios defined by different patterns of uric acid, phosphate, and potassium levels. Degree of TLS risk was found to be based on tumor type. Measures to mitigate risk and to treat CTLS are clearly defined and have been the subject of recent high-impact journal articles.

NCI supports ongoing efforts addressing TLS. An NCI-supported Children's Oncology Group trial focusing on Burkitt lymphoma evaluated prevention of high risk TLS with a new agent called rasburicase. With the use of rasburicase, only four percent of these high-risk patients developed CTLS. Additionally, renal impairment due to pre-treatment TLS improved in the week following initial treatment with rasburicase. Ongoing NCI intramural research is evaluating experimental therapy that may maintain or even improve cure rates for Burkitt lymphoma while decreasing toxicity, including CTLS, substantially.

The NCI Cancer Therapy Evaluation Program includes updated information and discussions regarding TLS within the relevant disease specific steering committees as a means of ensuring that clinical trials are based on best recent data, such as that for rasburicase and TLS outlined above. The goal of continuing to translate new information into standard clinical practice that may improve treatment for and decrease the risk of CTLS will be informed by ongoing clinical trial outcomes and by continually updating the information gained from ongoing studies, including those supported by NCI.

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National Heart, Lung, and Blood Institute (NHLBI)

Senate Significant Items

Item

Asthma. - The Committee continues to urge NHLBI to increase research on and awareness of asthma, and to collaborate with the FDA, NIAID, NICHD, NIMHD, and OMH in this regard. (p. 80)

Action taken or to be taken

NHLBI has for many years supported extensive research to improve treatment approaches for asthma and to explore opportunities for preventing its onset. The Asthma Clinical Research Network recently launched several trials, one to assess the effects of vitamin D supplementation for adults who have poorly controlled asthma, a second to evaluate the role of antibiotics and oral corticosteroids in managing acute respiratory infections and wheezing episodes in preschool children, and a third to compare the benefits of three different long-term treatment strategies for preschool children who have frequent wheezing episodes. A new phase II clinical trial was recently funded to study the use of continuous positive airway pressure to treat asthma. These studies are likely to expand the treatments available to help patients who have asthma, a critical need in light of growing evidence that considerable individual variations exist in disease manifestations and responses to treatment.

Genes play an essential role in asthma development and response to treatment. Asthma is more common and more severe in African Americans than in whites, yet the genetic basis for asthma in people of African descent has not been studied extensively. In fiscal year 2012, NHLBI funded a groundbreaking study, New Approaches for Empowering Studies of Asthma in Populations of African Descent, which seeks to identify all genetic variants associated with asthma in individuals with African ancestry. Through a new NHLBI program, Getting from Genes to Function in Lung Disease, a study is examining the role of an inflammatory gene (IL-33) in both asthma pathogenesis and possible immunity to parasitic disease. Discoveries from these genetic investigations will expand understanding of asthma development and stimulate formulation of treatments tailored to individual patients.

Collaboration with other NIH Institutes and Centers and Federal agencies provides opportunities to accelerate testing and refinement of asthma treatments. For example, NICHD includes NHLBI and NIAID in discussions about setting research priorities in its Best Pharmaceutical for Children program with the FDA and in research programs such as the recently announced Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems and Biomarkers: Bridging Pediatric and Adult Therapeutics.

NICHD is supporting research on factors present between conception and 2 years of age that may influence asthma development, such as nutrition, environmental exposures, infections, or injuries. Through the NIH-wide program Effect of the Social Environment on Health: Measurement, Method, and Mechanisms, investigators will examine the links between exposures to chronic and acute environmental stress by mothers and children and asthma biological

pathways and outcomes. Another NIH-wide program, Systems Science and Health in the Behavioral and Social Sciences, recently funded a study of the effects of neighborhood location on patient responses to asthma treatment. Results from these systems-based investigations will shed light on factors that contribute to asthma management and inform the design of comprehensive treatment approaches.

Development of methods to prevent the onset of asthma is an urgent priority. In addition to an on-going trial of vitamin D supplementation in pregnant women to prevent asthma in their offspring, NHLBI is funding two new studies of strategies to prevent wheezing in the first year of life, which may reduce susceptibility to asthma later in childhood. NHLBI collaborated with NIAID, NICHD, and NIEHS on a workshop to identify opportunities for asthma prevention. Another workshop will convene researchers from around the world who have followed cohorts of individuals since birth to identify ways to collaborate, pool data, and increase the scientific yield from their respective studies.

To increase awareness of asthma and effective treatments, NHLBI, NIMHD, NICHD, NIEHS, NIAID, FDA, OMH, and other Federal entities have developed the Coordinated Federal Action Plan to Reduce Racial and Ethnic Disparities in Asthma. Launched in May 2012, under the auspices of the trans-agency Task Force on Environmental Risks and Safety Risks to Children, the plan seeks to foster collaborative use of existing resources to promote comprehensive asthma management programs for high-risk children.

In addition, the NHLBI National Asthma Education and Prevention Program (NAEPP) has representatives from 16 Federal agencies as well as professional societies, patient advocacy groups, and nonprofit organizations who meet regularly to coordinate programs for increasing public awareness of asthma and educating clinicians, patients, and their families about best practices for its prevention and treatment. Through the NAEPP, many partnerships have been established to promote activities at the state and local community levels. This year, for example, programs have focused on web-based continuing medical education to improve training of clinicians and their staff, integration of asthma quality improvement tools in electronic medical records, and linking community health workers with clinical practices to help patients learn asthma management skills.

Item

Basic Behavioral Research Translation. - NHLBI is encouraged to speed the translation of basic research results in the behavioral and social sciences to clinical or other applications. (p. 80)

Action taken or to be taken

NHLBI has been a leader in translating basic behavioral and social science discoveries into new and effective health-related interventions. An early effort was the Translational Behavioral Science Research Consortia program, the result of a 2002 solicitation to stimulate application of findings from basic research to the development of innovative approaches for improving psychosocial and behavioral risk factors for heart, lung, blood, and sleep disorders. Two interdisciplinary projects were funded by the solicitation—one study used data from

fundamental research to develop an effective approach for treating heart disease patients who suffer from depression and the other developed an intervention, based upon research findings on positive feelings and self-affirmation, for motivating behavior change in patients with coronary artery disease, hypertension, or asthma.

In 2009, NHLBI funded the Obesity-Related Behavioral Intervention Trials (ORBIT) program, which supports interdisciplinary teams of basic and applied behavioral science researchers at seven research sites around the country. Led by NHLBI, in partnership with NCI, NIDDK, NICHD, and OBSSR, the program facilitates translation of discoveries from basic behavioral and social science research into innovative strategies to prevent and treat obesity. ORBIT investigators are developing interventions to promote healthy eating behaviors, decrease the desire for high-calorie foods, reduce stress-related eating, improve sleep patterns, and increase motivation to adhere to weight loss strategies. The program has provided a model for other NIH efforts to promote translational behavioral science, such as a 2010 program announcement titled Translating Basic Behavioral and Social Science Discoveries into Interventions to Improve Health-Related Behaviors. A collaborative effort involving NHLBI and eight other NIH components, the project uses findings from basic research on human behavior to develop interventions that promote healthy diets, physical activity, adherence to treatment, sun safety, and other healthy lifestyle behaviors.

In 2011, NHLBI funded a group of linked pilot studies to determine whether treatment of obstructive sleep apnea can influence risk of cardiovascular disease (CVD). The studies are expected to provide information about the feasibility of long-term positive airway pressure treatment in patients at risk of CVD and to evaluate the treatment's effects on markers of CVD risk.

NHLBI has also been a key participant in the trans-NIH Basic Behavioral and Social Science Opportunity Network (OppNet) initiative, which supports activities to advance understanding of behavioral and social systems and explore translational opportunities. NHLBI has taken the lead on four OppNet initiatives that resulted in a number of OD-funded applications addressing basic and translational behavioral science in heart, lung, blood, and sleep disorders.

Item

Cardiovascular Disease. - The Committee continues to believe that research on heart disease, stroke, and other forms of cardiovascular disease should be a top priority for NIH. Given promising cardiovascular scientific opportunities and projected escalating costs and prevalence, the Committee strongly urges NHLBI to boost funding for its cardiovascular portfolio to further support studies that will build on past accomplishments and enhance prevention and treatment efforts. In particular, the Institute should aggressively focus on and expand current cardiovascular research and actively invest in novel areas, including initiatives highlighted in its Division of Cardiovascular Diseases Strategic Plan. (p. 80-81)

Action taken or to be taken

As has been the case since its inception, NHLBI is strongly committed to supporting a robust portfolio of research to improve diagnosis, treatment, and prevention of cardiovascular disease (CVD).

Seven topics are identified as having especially high priority:

- New biological pathways, including actions of the microbiome (the microbial communities that inhabit the human body).
- Innovative treatment models, including use of anti-inflammatory agents for secondary prevention of CVD.
- Diagnostic imaging, including development of nanotechnologies and support of trials to determine the usefulness of newer imaging technologies.
- Device technologies, including circulatory support devices for infants and for patients with severe heart failure.
- Comparative effectiveness, including support for a trial on the value of invasive coronary angiography and revascularization in patients with stable angina and documented ischemia.
- Clinical outcomes, including assessment of hypertension outcomes in a very large cohort of patients enrolled in integrated health plans.
- Project management, including development of innovative low-cost methods for conducting large-scale CVD trials.

Approximately 62 percent of the Institute's FY 2012 extramural investment addresses CVD directly. In addition, substantial research carried out through the Institute's blood diseases and resources program is highly relevant to CVD, as a very large proportion of heart attacks and strokes are precipitated by thrombosis. NHLBI collaborates on some of its CVD research with other NIH components and HHS agencies, including CDC and FDA. Significant efforts are being made to enhance connections between basic and clinical studies through translational research that relies upon the collaborative efforts of multidisciplinary teams. NHLBI continues to support the Cardiovascular Cell Therapy Network, the Cardiothoracic Surgery Network, and the Progenitor Cell Biology Consortium, as well as the highly productive Pediatric Heart Network. Translation also focuses on application of clinical trial results to "real world" populations. NHLBI-funded researchers recently published findings from an observational study of nearly 200,000 patients with multi-vessel coronary disease; compared with coronary artery stenting, coronary artery bypass surgery was associated with lower long-term mortality.

Since the establishment of the Framingham Heart Study in 1948, NHLBI has supported large cohort studies to understand CVD risk factors and suggest approaches for prevention. Newer cohort studies focus on minority populations, including African Americans (the Jackson Heart Study and the Coronary Artery Risk Development In Young Adults Study), Hispanic Americans (the Hispanic Community Health Study–Study of Latinos), and Asian Americans (the Multi-Ethnic Study of Atherosclerosis). During FY 2011 and FY 2012, the highly productive Atherosclerosis Risk in Communities study initiated a new examination of about 9,000 surviving participants—all of whom are now over the age of 70—that is expected to provide critical insights about the development, progression, and treatment of heart failure, a major epidemic in our rapidly aging population.

Item

Chronic Obstructive Pulmonary Disease [COPD]. - The Committee applauds NHLBI for its plans to host a forum of stakeholders and representatives from Federal agencies to share information about current activities related to COPD and discuss the development of a national action plan to address this disease, the third highest cause of death in the United States. The Committee requests an update in the fiscal year 2014 congressional budget justification. (p. 81)

Action taken or to be taken

NHLBI continues to provide strong leadership for research and education to address the public health burden of COPD in collaboration with other components of the Federal government. Invited participants to the forum, planned for May 2013, will include the Surgeon General and representatives from AHRQ, FDA, CDC, CMS, VA, EPA, NOAA, and various NIH components that support COPD-related research such as NIA, NIDA, NCI, and NIEHS. Forum attendees will discuss the current involvement of Federal agencies in activities related to COPD, the scope and breadth of existing programs, the opportunities for increased cooperation and enhanced effectiveness of the Federal response to COPD, and the possibility of developing a national action plan for COPD. Consideration will also be given to developing and then providing regular updates to a document that summarizes Federal COPD activities. A final topic of discussion will be the merits of establishing a standing Federal group to assess and coordinate governmental activities related to COPD. NHLBI anticipates that improved communication among Federal agencies may ultimately lead to broader interactions involving other stakeholders, including patients and their representatives, and more effective approaches to address COPD nationwide.

Item

Jackson Heart Study. - The Committee recognizes that the Jackson Heart Study in Jackson, Mississippi, as authorized in the PHS Act, is the largest investigation of cardiovascular disease in the African-American population. The Committee acknowledges the continued need for comprehensive research at NHLBI and NIMHD to address this disease in African Americans and the important implications for such research to all persons threatened by cardiovascular disease. (p. 81)

Action taken or to be taken

The Jackson Heart Study (JHS) was initiated in 1998 to characterize cardiovascular disease (CVD) and the factors that influence its development and manifestations in African Americans, with the ultimate goal of identifying preventive approaches that could be particularly effective in that vulnerable population. The JHS has confirmed the high prevalence of obesity, hypertension, and CVD in African Americans and greatly enriched our understanding of associated risk factors. For example, the study found that a typical “Southern” diet is associated with fat in the liver, which in turn raises risk of diabetes; with coronary artery calcium, a sign of atherosclerosis; with measures of adiposity, including potentially harmful fat deposits on heart muscle; with diminished lung function; and with abnormal sleep patterns. The JHS has also facilitated identification of genes related to high blood pressure, high blood cholesterol, diabetes, and coronary heart disease. NHLBI has solicited proposals to renew the JHS contracts through 2018, as well as applications for new grants to expand analysis of JHS data. In support of its

mission to improve minority health and reduce health disparities, NIMHD has been a major partner in funding the JHS since the study's inception.

Forty percent of African American adults have hypertension, a major contributor to high rates of stroke, heart failure, and kidney failure, and NHLBI has for many years focused significant research attention on the condition. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in which 36 percent of participants were African American, was completed in 2003 but NHLBI continues to follow participants and analyze the data. The new Systolic Blood Pressure Intervention Trial (SPRINT) is evaluating the benefits of maintaining systolic blood pressure at less than 120 mm Hg in adults at particular risk of heart or kidney disease. Thirty percent of study participants will be African Americans. NHLBI recently supported a set of trials that tested new interventions—including engagement of pharmacists or visiting nurses, use of 24-hour ambulatory blood pressure monitoring and feedback, and incorporation of telemanagement—to improve hypertension control rates in African Americans. Although funding ended in June 2012, the investigators continue to collaborate and publish their findings.

NHLBI is particularly interested in supporting research to understand the genetic underpinnings of hypertension. As an example, a grant to Morehouse School of Medicine titled Vascular Epigenome Dynamics in African-American Hypertensives is exploring whether the chronicity and progression of vascular disease in hypertension is mediated by increased activity of pathological genes, as well as dampened activity of protective genes, that influence the blood vessels. This project will test the hypothesis that the expression of such genes is modulated by epigenetic marks or codes that are responsive to changes in dietary nutrients.

On a broader scale, NHLBI is supporting a series of genetics research projects focused on African Americans. In collaboration with researchers supported by several NIH components and drawing heavily from NHLBI-supported cohort studies that include up to 30,000 African Americans, several recent advances have been reported. They include the discovery of a gene associated with atrial fibrillation and the creation of a genetic “map” that will serve as a platform for future work. NHLBI has also supported the Exome Sequencing Project, which seeks to discover genes and mechanisms contributing to heart, lung, and blood disorders and includes genomes from 2,300 African Americans.

NHLBI is collaborating with NCI to support Centers for Population Health and Health Disparities. Centers in Baltimore, Chicago, and North Carolina are studying more than 30,000 African Americans in trans-disciplinary investigations of the social, behavioral, biological, and genetic determinants of disease.

NHLBI is committed to training and supporting the next generation of researchers who will focus on health disparities. The Programs to Increase Diversity among Individuals Engaged in Health-Related Research (PRIDE), an NHLBI initiative, promotes scientific career development of young faculty from diverse backgrounds by providing opportunities for focused mentorship and extensive networking.

Item

Lymphangi leiomyomatosis [LAM]. - The Committee remains very interested in efforts to find a cure for LAM, a progressive and often fatal lung disease in women. The Committee supports both intramural and extramural means of expanding research on LAM and urges NHLBI to use all available mechanisms as appropriate, including Translational Program Project Grants, to stimulate a broad range of clinical and basic research. The Committee commends NIH for supporting multicenter LAM trials and encourages additional support of such trials. (p. 81)

Action taken or to be taken

NHLBI continues its support of research to improve the outlook for patients with LAM using a variety of mechanisms and approaches. Projects under way address a range of topics, including exploratory studies in a mouse model to test the theory that LAM cells originate in the uterus and then migrate to the lung.

Last year, the Multicenter International Lymphangi leiomyomatosis Efficacy of Sirolimus (MILES) trial demonstrated that treatment with sirolimus, an immunosuppressant drug used to prevent rejection of organ transplants, can slow progression of pulmonary LAM. However, deterioration in lung function resumed upon discontinuation of the treatment. Because sensitivity to sirolimus varies and the drug has significant side effects (e.g., lung inflammation) that are particularly worrisome in LAM patients, other therapeutic options are being investigated. LAM's cancer-like behavior suggests that multi-drug therapy will be required.

The effort to discover new treatments includes an investigation into the key pathways and mechanisms by which the tuberous sclerosis complex 2 (TSC2) gene, which malfunctions in LAM patients, regulates LAM cell adhesion, migration, and invasiveness. Based upon insights derived from that work, researchers have identified targets for multi-drug therapy that may prevent or stop tumor growth. A combination therapy with two drugs that are already FDA-approved for clinical uses—sirolimus and simvastatin, a cholesterol-lowering agent—is being tested in a new mouse model that mimics some features of human LAM. Other research is determining the role of reproductive hormones in development and progression of the disease; prolactin, for instance, has been found to stimulate growth of LAM cells and is being studied as a potential drug target.

NHLBI intramural investigators are using computed tomography chest scans of LAM patients and histopathological analyses of their lung tissue to detect textural abnormalities and investigate their correlations with deficits in pulmonary function and progression of disease. The research is seeking to uncover additional treatment targets, identify molecular markers, and determine the mechanisms of lung destruction.

The Institute continues to support a LAM tissue repository; provide co-funding for the annual LAM scientific conference, now in its 12th year; participate in meetings of the trans-NIH Tuberous Sclerosis Coordinating Committee; and encourage investigators to submit applications to conduct clinical trials in LAM.

Item

Marfan Syndrome. - The Committee commends NHLBI for its leadership of the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions Registry [GenTAC]. The Committee encourages the Institute to use GenTAC to advance research on surgical outcomes for Marfan syndrome patients who undergo different procedures to repair compromised aortas and valves. (p. 81)

Action taken or to be taken

The NHLBI-supported GenTAC was established as a resource to advance the treatment of patients with genetically triggered thoracic aortic aneurysms. The original program, awarded in September 2006, assembled a biorepository of materials and data from 2,000 patients who were enrolled through five participating centers. With feasibility established, GenTAC was renewed in September 2010 with an expanded program to enrich datasets by collecting longitudinal follow-up data, adding imaging and phenotyping capabilities, and conducting limited new enrollment of patient subgroups of high scientific interest. To date, more than 3,000 patients have been enrolled, including more than 800 patients with Marfan syndrome. The project is currently planned to be supported through 2016 and has established policies for use of its data and biospecimens by the research community.

GenTAC is already proving its worth as an important resource to enable research. Investigators have published data on the results of surgical treatment of enrolled participants, including long-term outcomes of aortic surgery in patients with Marfan syndrome. GenTAC biospecimens have also provided essential material for research on the dysregulation of transforming growth factor- β in Marfan syndrome and recurrent chromosome duplications as risks for aortic dissection.

NHLBI welcomes meritorious investigator-initiated projects that leverage GenTAC resources to assess various surgical approaches in Marfan syndrome. NHLBI and the GenTAC leadership are committed to engaging potential applicants through the project's website (<http://gentac.rti.org>), through publications in peer-reviewed journals and mentions at scientific meetings (e.g., the international Aortic Summit, held in August 2012), and through collaborations with patient-advocacy groups such as the National Marfan Foundation, the Ehlers-Danlos National Foundation, and the Turner Syndrome Society.

Item

Pediatric Cardiomyopathy. - The Committee commends NHLBI for its commitment to pediatric cardiomyopathy research and urges the Institute to maintain support of the Pediatric Cardiomyopathy Registry and Pediatric Cardiomyopathy Specimen Repository. The Committee encourages NHLBI to establish a pediatric cardiomyopathy task force that will focus on defining standards of care, identifying gaps in basic and clinical research, developing a research agenda, and working towards better genetic screening methods. (p. 81)

Action taken or to be taken

NHLBI is strongly committed to pediatric cardiomyopathy research and continuously identifies gaps and opportunities in basic and clinical research in the area through on-going grant portfolio reviews and conversations with investigators and patient-advocacy groups. Recently, for

example, NHLBI staff had a productive discussion with the Children's Cardiomyopathy Foundation that is expected to lead to continuing engagement in developing a research agenda.

NHLBI supports work that directly and fully leverages the Pediatric Cardiomyopathy Registry (PCMR) and the companion Pediatric Cardiomyopathy Specimen Repository. The PCMR already contains clinical data from more than 3,500 children seen at multiple centers, and the Institute recently funded a large project that will enroll additional children. The new project will also seek to identify genes that may predispose children to develop cardiomyopathy, examine interactions between genes and patient characteristics that may shed light on appropriate care for the children, and use state-of-the-art technology to develop better genetic screening tools. NHLBI-supported investigators are also working to correlate biomarkers with clinical outcomes in PCMR patients, using specimens available in the Repository.

An additional strategic component of NHLBI's portfolio of pediatric cardiomyopathy research is the initiative Pumps for Kids, Infants, and Neonates (PumpKIN). Funded in 2010 as an extension of the NHLBI Pediatric Circulatory Support Program, it supports development of innovative ventricular assist devices for infants and young children with congenital or acquired heart disease, many of whom have cardiomyopathy. Such devices are intended to maintain blood circulation while patients recover function or await heart transplantation.

NHLBI supports basic science research to understand the mechanisms involved in the development of cardiomyopathy, including evaluation of structure and function in genetically engineered mouse models of early muscular dystrophy. Other basic investigations are using gene therapy to reverse cardiomyopathy in dog models of Duchenne muscular dystrophy.

The Institute in concert with the extramural community acts to identify research gaps and refine the research agenda for pediatric cardiomyopathy. In addition, it continues to fund exciting new science that will help identify better genetic screening methods. Thus, current activities are fulfilling three of the four elements of the suggested task force. The fourth, defining standards of care, is not squarely within NHLBI's purview although it could play an informative role in any effort to do so.

Item

Pulmonary Fibrosis. - The Committee supports ongoing efforts to study pulmonary fibrosis and notes the promising strategy of researching fibrosis across organs. The Committee encourages NHLBI to develop a strategy for enhancing research on this disease. (p. 81)

Action taken or to be taken

NHLBI supports an extensive portfolio of research on pulmonary fibrosis (PF). Investigator-initiated basic science projects are defining the roles of various types of lung cells in the development of PF, identifying environmental and infectious agents that could cause PF in susceptible individuals, and investigating biological markers that may enable early diagnosis of PF and accurate prognostic assessment.

NHLBI also supports targeted research activities such as the Idiopathic Pulmonary Fibrosis Clinical Research Network that conducts controlled clinical trials of multi-drug regimens and promising new therapeutic agents in patients with newly diagnosed idiopathic PF, in which by definition, the cause of the fibrosis is not known. Broader pulmonary research initiatives of relevance to PF include the Lung Tissue Research Consortium to collect, prepare, and distribute lung tissue for research; the Centers for Advanced Diagnostics and Experimental Therapeutics (CADET-1) to accelerate translation of basic science research discoveries to clinical use; and the Phase II Clinical Trials of Novel Therapies for Lung Diseases to assess the safety and efficacy of emerging treatment modalities.

NHLBI encourages the study of fibrosis across organ systems, an approach that promotes research efficiency by allowing fibrosis researchers to share valuable resources and offers the possibility that many patient groups will share the eventual benefits of discoveries. The Institute provides a number of support mechanisms (e.g., program projects) to facilitate interactions among investigators from diverse research disciplines who are studying fibrosis in lung, kidney, heart, liver, and other organs.

In November 2012, NHLBI convened a workshop to develop a strategic plan for PF research. Representatives from NIH, pharmaceutical companies, the FDA, and patient advocacy groups joined PF researchers to discuss research priorities and potential collaborations. We expect to submit the report to the Annals of the American Thoracic Society (AnnalsATS) for review in April.

Item

Scleroderma. - The Committee encourages NHLBI to support additional research on the impact of connective tissue diseases, such as scleroderma, on the pulmonary system. (p. 81)

Action taken or to be taken

Pulmonary complications constitute a major burden for patients with connective tissue diseases. For example, pulmonary fibrosis and pulmonary arterial hypertension are the leading causes of mortality in patients with scleroderma. NHLBI is committed to continuing its support for research in this area and to capitalizing on emerging scientific opportunities. The Institute currently supports a clinical trial comparing the effectiveness of two immunosuppressive drugs in treating pulmonary fibrosis in scleroderma. Other research is exploring the complex remodeling that occurs in the pulmonary blood vessels and right ventricle that leads to high morbidity and mortality in scleroderma patients with pulmonary arterial hypertension. Several broad-scope initiatives in NHLBI lung diseases portfolio, such as Phase II Clinical Trials of Novel Therapeutics for Lung Diseases and Translational Program Projects, provide ongoing mechanisms to support research to reduce the pulmonary complications of connective tissue diseases.

Item

Sickle Cell Trait. - The Committee commends NHLBI for its efforts to develop a research agenda on sickle cell trait and its relation to exertion-related illness and other conditions. The Committee encourages the Institute to reach out to medical societies in hematology and sports medicine, as well as athletic associations, to collaboratively develop and undertake research that can inform current policies related to sickle cell trait screening and participation in athletic activities. (p. 81-82)

Action taken or to be taken

Historically, health professionals have not regarded sickle cell trait (SCT) as a disease or medical condition requiring intervention other than counseling about childbearing decisions. Although it does not appear to cause adverse health effects in the vast majority of the 2.5 to 3 million people in the United States who have it, recent reports of sudden or exercise-related deaths and serious illnesses in some individuals with SCT have raised concerns that it may increase the risk of certain health problems.

Against this backdrop of uncertainty, NHLBI is working with a number of organizations to develop a research agenda on SCT. The Institute was an active participant in the planning and conduction of a 2009 CDC meeting on public health implications of SCT. In 2010, NHLBI convened the workshop *Framing the Research Agenda for Sickle Cell Trait* to review information about the clinical manifestations of SCT, discuss reports of exercise-related sudden death, and examine the public health, societal, and ethical implications of policies regarding SCT. Workshop speakers and attendees represented academia, CDC, HRSA, NHGRI, healthcare providers, sports medicine professionals, and other interested parties. In January 2012, NHLBI participated in an expert panel meeting convened by the American Society of Hematology to discuss testing for SCT.

A major research opportunity identified at the 2010 NHLBI workshop was the conduct of a large epidemiological study to improve understanding of SCT and its possible health risks. In response, NHLBI has initiated a collaboration with experts (epidemiologists, medical examiners, and sports medicine physicians) at the Department of Defense (DoD) and the Uniformed Services University of the Health Sciences to conduct such a study. Researchers will use existing validated DoD databases to examine the healthcare use of persons with SCT versus those without it. The effort will include identification of existing data sources, retrieval and merging of data, exploratory analyses of data on SCT-associated morbidity and mortality, creation of a surveillance system for SCT-related diagnoses and sudden or exercise-related deaths, and selection of end points (e.g., specific medical diagnoses). This initial effort will facilitate the planning of prospective studies to identify factors that may contribute to SCT-associated sudden or exercise-related death, understand exercise intensity and its relationship to exercise collapse, explore the physiological responses to exercise in persons with SCT, evaluate SCT as an independent risk factor for exercise-related collapse, investigate red blood cell sickling during exercise, study vascular function, and assess health outcomes.

Item

Sleep Disorders. - The Committee applauds NIH's Sleep Disorders Research Plan, published by the National Center on Sleep Disorders Research. The Committee urges the Institute to work with other ICs to implement the plan's recommendations for improving sleep research and training, and for advancing multi-Institute collaborations. (p. 82)

Action taken or to be taken

NHLBI, through the National Center on Sleep Disorders Research (NCSDR), coordinates sleep research and training throughout NIH as outlined in the 2011 NIH Sleep Research Plan. The Institute works with other NIH components to implement the plan through targeted solicitations and support for an array of ancillary studies and pilot clinical trials. Ongoing NHLBI collaborations include the following:

- A study of sleep and sleep apnea conducted within an NIDDK-funded clinical trial of weight loss to reduce risk of cardiovascular disease (CVD) in obese patients with diabetes.
- A study of sleep and sleep apnea conducted within an NICHD-funded study of maternal CVD risk during pregnancy.
- A study of the influence of poor sleep on the health of elderly community-dwelling men conducted within an NIA/NIAMS-funded study of osteoporotic fracture risk. NIAMS supports parallel research in elderly women.

A multi-Institute collaboration, the NIH Basic Behavioral and Social Science Opportunity Network (OppNet), has yielded a diverse range of sleep research funding opportunities, including support for meetings of interdisciplinary research teams and grants to study sleep and the social environment.

A collaborative effort of NHLBI and NICHD in fiscal year 2012 addresses innovative education research in sleep health and circadian biology. The initiative seeks to stimulate development of teaching tools, platforms, and programs to enhance the training of researchers, educators, and healthcare providers in sleep disorders and circadian biology.

A milestone in NIH support for sleep research training was achieved in fiscal year 2012 with the funding of seven institutional National Research Service Awards at six institutions, including a new award at Morehouse School of Medicine, one of the nation's Historically Black Colleges and Universities.

NHLBI leads an NIH working group supporting national objectives for sleep health in the HHS Healthy People 2020.

During fiscal year 2013, monthly meetings of the trans-NIH Sleep Research Coordinating Committee and a public meeting of the Sleep Disorders Research Advisory Board will be convened to assess progress on the NIH Sleep Research Plan and facilitate NIH-wide scientific collaborations.

Item

Stem Cell Biology. - The Committee encourages NHLBI to support additional research in the development of blood stem cells from induced pluripotent stem [iPS] cells and to address barriers to the clinical translation of iPS cell technology. (p. 82)

Action taken or to be taken

Pluripotent stem cells offer tremendous promise as tools for disease modeling and drug screening. They also are potential future sources of patient-specific matched cells that might be used in cell-replacement therapies for many different diseases. NHLBI supports a large portfolio of both solicited and investigator-initiated projects in iPS cell research. The NHLBI Progenitor Cell Biology Consortium Research Hubs comprise clusters of synergistic research projects to identify and characterize progenitor cell lineages, to direct the differentiation of stem and progenitor cells, and to develop new strategies addressing the unique challenges presented in transplanting them. The Consortium supports studies of the pathways governing iPS cell differentiation into cardiac, pulmonary, and hematopoietic stem and progenitor cell types. It encourages the development of new technologies for creating iPS cells that do not entail the use of either oncogenes or retroviral vectors and their attendant risks, knowledge that will further the development of blood stem cells from iPS cells.

NHLBI also supports collaborations of multidisciplinary teams to catalyze research on lung cell therapy through a “Building the Foundation” initiative of the Lung Repair and Regeneration Consortium. One of the Lung Consortium’s goals is to apply iPS cell technology, which is not yet used widely in pulmonary research, to further the field of regenerative therapies for the lung.

An NHLBI program announcement, Translation of Pluripotent Stem Cell Therapies for Blood Diseases, is inviting applications for the development of new technologies needed to use stem cells in the future cell therapies to treat sickle cell disease and other blood disorders. Its focus is on two key areas that are impediments to further progress—the development of techniques to generate sufficient numbers of clinical grade hematopoietic cells for evaluation in human subjects and development of protocols that enable the efficient engraftment of hematopoietic cells derived from pluripotent stem cells or via cellular reprogramming. This research that will directly address the derivation of blood stem cells from iPS cells is being implemented in collaboration with the ongoing NHLBI Progenitor Cell Biology Consortium.

Research teams have derived patient-specific iPS cells that will serve as new cellular disease models for future research. Other teams have performed comprehensive phenotypic, functional, and molecular comparisons of multiple human cell lines and observed interesting differences in DNA methylation patterns. These differences may provide important insights into these cellular models and the reprogramming process itself, which converts a skin or blood cell into an iPS cell with its stem cell-like properties.

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National Institute of Dental and Craniofacial Research (NIDCR)

Senate Significant Items

Item

Temporomandibular Disorders [TMD]. - The Committee recognizes the advances that have been made as a result of NIDCR funding toward understanding the pain associated with TMD and encourages the Institute to continue basic and clinical research in this area. The Committee also encourages NIDCR to collaborate with other ICs regarding the etiology and pathogenesis of TMD as well as the co-morbid chronic pain conditions and disorders that solely or predominately affect women. An under-researched aspect of these disorders is the jaw joint. NIDCR should work with NIAMS and NIBIB to develop research opportunities in the area of joint pain and dysfunction. Topics that need further research include: the kinematics and biomechanics of the jaw in normal and disease states; the development of biomarkers in bone, muscle, and cartilage that are predictive of temporomandibular disease progression; the interactions of the temporomandibular joint musculoskeletal system with the nervous system; and the development of non-invasive measures of temporomandibular joint bone, cartilage, and muscle structure, degradation, and repair. The Committee urges NIDCR, NIAMS, NIBIB, and other relevant ICs to organize a workshop to assess the state of the science and identify research gaps and future scientific directions to advance understanding of the temporomandibular joint. (p. 82)

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. The disorder also may strike people who are suffering from other chronic pain conditions. The overarching goal of the NIDCR TMJD and Orofacial Pain Program is to enable better prevention, treatment, and diagnosis of orofacial pain disorders, with a focus on understanding the mechanisms underlying the transition from acute to chronic pain states and the development of new pharmacological and behavioral interventions to prevent or reverse the transition.

In one example of the progress we have made toward these goals, NIDCR funded the first large multi-site longitudinal study of TMJD in the hopes of identifying biological, psychological, and social factors that increase the risk of developing TMJD and chronic TMJD. This study, Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA), recently issued its preliminary findings, showing that incidence of chronic TMJD increases with age and does not correlate with socio-economic status, unlike in some other pain conditions. Importantly, certain genetic factors were found to be associated with TMJD. Findings from the first seven years of study were published in the November 2011 special issue of *The Journal of Pain*, and we are confident that the final results will prove seminal in the study of chronic orofacial pain. Building on this study, NIDCR will support research defining the genomics of chronic orofacial pain, focusing on identifying gene variants that influence pain perception, their environmental triggers, and their effect on a patient's outlook and behavior. Newly funded research also will work to identify risk factors for co-occurring chronic pain conditions.

NIDCR continues to support research on a wide range of topics concerning the basic biology and physiology of the temporomandibular joint in health and disease. Ongoing projects are addressing the cell biology of nutrient transport in the TMJ disc, the degeneration and regeneration of TMJ cartilage and disc, the role of sex hormones in TMJ cartilage and bone development and degeneration, and the biomechanics and loading forces of the joint as risk factors for development of temporomandibular joint disorders.

NIDCR actively seeks to work across NIH to advance research on TMJD and other chronic pain conditions that frequently co-occur and disproportionately affect women. These efforts include leading the fall 2011 formation of a new trans-NIH working group, the Overlapping Chronic Pain Conditions Working Group, to help coordinate and advance these areas of research. This working group, in partnership with academic and advocacy communities, held a two-day workshop on overlapping chronic pain conditions on August 13-14, 2012 on the NIH Campus.

To complement these efforts, NIDCR, NIAMS and NIBIB have agreed to organize a joint workshop or scientific meeting on the topic of primary interest to the Committee – the temporomandibular joint. All three Institutes' priorities and expertise are highly relevant to investigating this unique joint. For example, NIBIB supports early stage research on new approaches to generate and monitor engineered tissues to restore or replace damaged ones, and recent advances in imaging technology will allow much better access to the TMJ. In addition to the many NIAMS-funded projects related to joint physiology and arthritis, NIAMS supports a range of basic, translational and clinical studies on chronic pain conditions that could help inform TMJD research directions. NIDCR, NIAMS and NIBIB worked closely with the TMJ Association to define the goals of this meeting, which is scheduled to take place on May 3, 2013.

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

Senate Significant Items

Item

Burden of Digestive Diseases. - Due to advancements in diagnosis and greater understanding of many digestive conditions, the Committee requests that NIDDK update its report on the burden of digestive diseases in the United States to provide more accurate information on the current economic and health impacts of these conditions. (p. 82-83)

Action taken or to be taken

The 2008 report entitled “*The Burden of Digestive Diseases in the United States,*” was prepared to accompany the research plan entitled “*Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases.*” This research plan was a substantial, trans-NIH effort with a 10-year time horizon. It was informed by the burden of digestive diseases report developed in parallel during the multi-year research planning process. The burden of disease report and research plan are available in hard copy and electronic form on the following websites:

<http://www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/BurdenOfDisease/DigestiveDiseases/> and

<http://www2.niddk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/NCDD/FinalResearchPlanPosting.htm>.

NIDDK, together with other NIH Institutes and Centers whose missions relate to digestive diseases, supports a robust research portfolio that has contributed to important advances in understanding, diagnosing, treating, and preventing these diseases. This digestive diseases research portfolio aligns with the goals and recommendations of the National Commission on Digestive Diseases’ research plan, which is based on information in the 2008 report on the Burden of Digestive Diseases in the United States.

NIDDK produced the 2008 burden of disease report and a similar report in 1994. The updated 2012 report on the burden of digestive diseases in the United States that the Committee requested has been published (<http://www.ncbi.nlm.nih.gov/pubmed/22885331>). This report was partially funded by NIDDK. Thus, there is no need to duplicate the work contained in the recently published report. However, NIDDK will pursue plans for preparing information on recent advances in digestive diseases research, as an adjunct to the Gastroenterology report.

Item

Chronic Pelvic Pain. - Interstitial cystitis often coexists with several poorly understood and neglected chronic pain conditions. The Committee applauds the progress made by the Institute to understand the overlapping nature of these disorders through the Multidisciplinary Approach to the Study of Chronic Pelvic Pain [MAPP] Research Network. NIDDK is encouraged to continue its focus on understanding co-morbidity in the second phase of the MAPP project. (p. 83)

Action taken or to be taken

The multi-center MAPP Research Network is conducting innovative, collaborative studies of the two most common urologic chronic pelvic pain conditions (UCPPS)—interstitial cystitis/painful bladder syndrome (IC/PBS), and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Since its inception, the Network’s unique approach has entailed searching “beyond the bladder/prostate” to find the causes of these conditions, including studying the possible relationships between these conditions and other chronic pain disorders, such as irritable bowel syndrome (IBS), fibromyalgia, and chronic fatigue syndrome. Groups of patients displaying these co-morbid disorders are being recruited and characterized within the current, ongoing efforts of the Network. At the same time, NIDDK is moving forward with plans for a second phase of the MAPP Research Network, once the current phase is completed. It is anticipated that the relationships between UCPPS and co-morbid conditions will continue to be investigated in the Network’s second phase. This research is likely to include additional, novel epidemiologic studies, as well as additional assessments of the origin and cause(s) of pain and underlying causes of symptom variation, e.g., symptom “flares,” in people with these conditions. It is hoped that such efforts will continue to elucidate both UCPPS and co-morbid conditions and provide a foundation for development of new therapeutic strategies for persons living with these pain syndromes.

In related efforts, NIDDK is a member of the Trans-NIH Pain Consortium, which promotes collaboration across the many NIH Institutes and Centers that have programs and activities addressing pain. In August 2012, the Consortium sponsored a scientific workshop focused on chronic overlapping pain conditions, which was co-chaired by the chair of the MAPP Research Network. Efforts such as these will also help to advance research strategies to address the causes, course, and diagnosis of pain conditions co-morbid with IC/PBS.

Item

Diabetes Prevention. - The Committee applauds NIDDK for its continued efforts to build on the successes of the Diabetes Prevention Program and encourages the use of additional resources to improve prevention and treatment of diabetes in order to bring the Nation closer to a cure. (p. 83)

Action taken or to be taken

Landmark NIDDK diabetes prevention and treatment studies have greatly improved the lives of people with diabetes: life expectancy of people with type 1 diabetes has increased by 15 years in the last few decades, and the proportion of people with either major form of diabetes who will go on to need an amputation or develop kidney failure is decreasing. NIDDK’s Diabetes Prevention Program (DPP) showed that lifestyle changes to achieve modest weight loss can reduce the incidence of type 2 diabetes by over half at 3 years of age. The intervention helps stave off diabetes for at least 10 years and substantially improves quality of life for those who receive it. While the lifestyle change intervention was cost effective in the DPP, the Institute is building on this success in several ways, including investment in translational research to further amplify the cost-effectiveness and increase the accessibility of behavioral interventions to prevent diabetes. Several such projects have shown great promise. The encouraging results from these NIDDK-supported translational efforts have led CDC to create a program to train and certify a workforce

of lay lifestyle interventionists to deliver a group form of the DPP lifestyle intervention. Some private insurers are now covering these services, recognizing the potential not only to benefit their patients' health, but also to reduce overall costs. The DPP Outcomes Study continues to yield valuable data on diabetes prevention, and the genetics and natural history of the disease.

Based on a promising pilot trial suggesting it may be possible to help prevent type 2 diabetes by optimizing the intake of vitamin D, NIDDK is supporting plans for a larger trial. The newly launched Lifestyle Interventions in Expectant Moms study (LIFE-Moms) will test several lifestyle interventions to control weight gain and prevent gestational diabetes. LIFE-Moms will also follow the women and their offspring up to 1 year after delivery to explore correlations between gestational weight gain and later metabolic status for both mother and baby. The critical public health imperative of type 2 diabetes prevention in youth is underscored by results of the Treatment Options for Type 2 Diabetes in Adolescents and Youth Study, which provided sobering insights on the difficulty of treating the disease in people who develop it while still young. The Type 1 Diabetes TrialNet is testing two interventions for type 1 diabetes prevention. Additional approaches to type 1 diabetes prevention may emerge from a major study to identify environmental triggers of the disease by following newborns at high genetic risk.

In addition, two new studies will help determine how best to treat adults recently diagnosed with type 2 diabetes. A major new multi-center study is being launched to compare four commonly used glucose lowering drugs and determine which, when added to metformin, is most effective in achieving and maintaining glycemic levels known to reduce long-term complications. The Restoring Insulin Secretion study will examine whether early aggressive therapy for people with prediabetes or new onset type 2 diabetes will preserve a capacity for insulin secretion.

NIDDK is funding research to uncover the physiological reason bariatric surgery can induce type 2 diabetes remission, and to study what factors influence success of this approach. Importantly, recent findings from the Beta Cell Biology Consortium have demonstrated that one day it may be possible to induce some of a person's own cells to "reprogram" into insulin secreting beta cells. These results and others from the Consortium suggest it may be possible to overcome diabetes in the future, achieving full or partial remission, by regenerating or replacing pancreatic beta cells.

Item

Fecal Incontinence. - The Committee commends NIDDK for its launch of the Bowel Control Awareness Campaign and recognizes that fecal incontinence significantly hinders the work and social lives of those affected. The Committee prioritizes research addressing this condition to improve patient quality of life and to meet the research goals indicated in the NIDDK report "Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases." (p. 83)

Action taken or to be taken

The Bowel Control Awareness Campaign is based on recommendations of the panel of experts convened for the "NIH State-of-the-Science Conference Statement on Prevention of Fecal and Urinary Incontinence in Adults," held in December 2007, to raise public awareness of incontinence and the benefits of prevention and management. Through its resources (available at

<http://www.bowelcontrol.nih.gov/>), the campaign continues to raise awareness, with the aim of improving the lives of men and women living with this condition.

The Institute also supports a robust research program focused on fecal incontinence. A recent advance from this program showed progress in using human cells to bioengineer a physiologically functional internal anal sphincter—one of the muscles that close the anus and thereby maintain fecal continence—and successfully implanting it into mice. Studies from this program meet research goals outlined in the report, “Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases,” such as the goal to “develop new devices, surgical techniques, or tissue replacement approaches to enhance fecal continence.” NIDDK’s research program in this area is also addressing several other research goals identified in the Commission’s report related to improving understanding and management of fecal incontinence.

Item

Functional Gastrointestinal Disorders [FGIDs]. - The Committee understands that FGIDs can dramatically impact children’s social and educational development, and encourages NIDDK to work with NICHD to support research addressing FGIDs in children. (p. 83)

Action taken or to be taken

NIDDK and NICHD share an interest in improving the quality of life for children who suffer from functional gastrointestinal disorders (FGID). Both Institutes collaborate closely, although most investigator-initiated grant applications are assigned to NIDDK, with NICHD serving in an ancillary funding role.

NIDDK is supporting research on the collective genetic material of microbes (the “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, scientists have identified microbial “signatures” associated with pediatric irritable bowel syndrome (IBS), and with subtypes of IBS with or without constipation. 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 environment might be modified to improve health outcomes and quality of life for children with these disorders.

NICHD supports research on FGIDs, which are characterized by chronic or recurrent abdominal symptoms without identifiable pathology, including funding grants for research designed to understand the biopsychosocial processes associated with pediatric chronic abdominal pain that place children at increased risk for FGIDs as adolescents and adults. One currently funded study will identify characteristics of youth with chronic abdominal pain who are most likely to experience psychiatric disorders as adolescents and young adults, suggesting factors that could be addressed in future prevention and treatment efforts. NICHD also supports a study that will evaluate a parent-only, social learning, and cognitive behavior therapy intervention, delivered in-person for one group, and by telephone for another group, aimed at reducing symptoms of

functional abdominal pain in their children. If successful, this intervention could provide useful models for the development of effective, accessible interventions for FGIDs and other medical problems.

Item

Inflammatory Bowel Disease. - 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 and its impact on pediatric patients. The Committee requests an update on this program in the fiscal year 2014 congressional budget justification. (p. 83)

Action taken or to be taken

NIDDK has worked closely with NHGRI in supporting the Human Microbiome Project (HMP). This research will contribute to advancing the understanding of inflammatory bowel disease (IBD) and its impact on pediatric patients. IBD is a complex genetic disease caused by inappropriate immune responses to microbes that naturally inhabit the human intestine, collectively known as the human microbiota. Therefore, identifying the communities of bacteria that populate the intestine and understanding the roles they play in human health and disease is crucial to developing treatments for adult and pediatric IBD. NIDDK has co-supported HMP studies in pursuit of this goal, including:

- A multi-year, multi-center project has established a population-scale framework to develop metagenomic protocols and has generated the largest, most comprehensive reference of human microbiome data associated with healthy adult individuals to date. In addition, a collection of biological specimens that represent the human microbiome and corresponding blood samples donated by study participants were collected. The information and specimens developed by this project provide a powerful resource for ongoing and future research.
- Another study has characterized the microbiomes of healthy adults in a Western population. The researchers found wide diversity, as well as strong metabolic specializations of microbe communities that occupied different body sites. Although the microbe communities that populated specific niches would vary, several metabolic pathways expressed remained constant among individuals and body habitats. These study results offer structural and functional information on the human microbiome which will provide firm footing for future epidemiological, ecological, and translational research.
- In a review of the virulent bacterium *C. difficile* and the gut microbiota, researcher scientists explored how microbes that normally populate the intestine interact with their human host to prevent pathogen colonization. Interactions between microbiota and host can result in expression of host products that control pathogen colonization and proliferation. Also, host recognition of microbiota-associated molecular patterns can trigger the host immune system to attack pathogenic bacteria. Because antibiotic therapy can change the structure and function of the gut microbiota, disturbing resistance to *C. difficile* colonization, treatment with antibiotics is identified as a major cause of infection by this organism.

- Research scientists conducted a study investigating the effect of a diet high in saturated fat. Using a mouse model that is susceptible to colitis, the researchers compared a diet high in milk-derived saturated fat with a diet high in polyunsaturated fat derived from safflower oil. Based on data from the study, the researchers presented a mechanism by which the Western diet, high in saturated fats, could increase complex immune-mediated diseases such as IBD.

Item

Interstitial Cystitis. - The Committee continues to encourage a focus on research and treatment relating to interstitial cystitis, which impacts individuals of all ages. The Committee encourages the inclusion of research focused on this disease in children as a part of these activities. (p. 83)

Action taken or to be taken

Interstitial cystitis/painful bladder syndrome (IC/PBS) remains a challenge for patients, physicians, and researchers, as it is a not-well-understood pain condition of unknown cause for which no fully effective treatment or prevention strategies are yet available. NIDDK spearheads NIH-supported research on IC/PBS with the goal of better understanding this condition so that researchers can develop effective preventive and therapeutic approaches. Current efforts include the Multidisciplinary Approach to Pelvic Pain (MAPP) Research Network, a Specialized Center of Research focused on irritable bowel syndrome (IBS) and IC/PBS, interdisciplinary research teams in IC/PBS, and diverse investigator-initiated research projects that are providing insights into potential causes and mechanisms underlying pelvic pain. NIDDK is also a member of the Trans-NIH Pain Consortium, which promotes collaboration across the many NIH Institutes and Centers that have programs and activities addressing pain. IC/PBS predominantly affects adult women, and recent epidemiology studies and analyses as well as clinician experience suggest that it is rare in children and is more prevalent in middle age than in youth and older age. This is supported by recruitment data for the MAPP Research Network, in which approximately 2 percent of persons who have enrolled in the MAPP Research Network with IC/PBS are children 18 to 21 years old. While the MAPP Research Network did not recruit nor enroll younger children with IC/PBS – mostly for reasons of practicability, as it is rarely diagnosed before adulthood – the issue of risk factors early in life that may increase susceptibility to IC/PBS is potentially important. Notably, the MAPP Research Network does collect information that dates back to childhood events. How to adequately study early risk factors and their relationship to IC/PBS, generally diagnosed in adulthood, remains a difficult challenge. It is hoped that current efforts to understand the condition will lead to improved diagnostic tools and strategies, and that this may facilitate future efforts to identify and appropriately include both children and younger adults with early IC/PBS in research that may benefit their health.

Item

Polycystic Kidney Disease [PKD]. - The Committee continues to urge 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 neoplastic diseases. For example, the Committee understands that Pioglitazone, a drug that may have potential for treating PKD, is being studied in Parkinson's patients and is partially funded through NINDS. (p. 83)

Action taken or to be taken

Previous studies have indicated that slow, constrained cyst growth results from changes in cellular architecture, fluid secretion, and non-cancerous cell proliferation. NIDDK supports studies focused on determining the mechanisms that drive cyst growth and therapies that slow or prevent this process. NIDDK has funded research to identify genes that determine the severity of the disease. The development and study of new animal models is leading to studies that will likely translate to human mechanisms and new therapies.

Two large NIDDK-funded clinical studies—HALT Progression of Polycystic Kidney Disease (HALT-PKD; a collaboration with industry, which supplies drugs) and Consortium for Radiologic Imaging Studies of PKD (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. 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 is testing the blockade of the renin-angiotensin system (a hormone system that regulates blood pressure and water balance) as a therapy for PKD and to demonstrate the validity of total kidney volume and other biomarkers as surrogates for progression of disease. Because kidney failure in this population does not occur prior to age 50-60 years, it is important that these studies are completed before new pharmaceutical trials are undertaken to provide qualified surrogate markers of this slowly progressive disease.

NIDDK has supported extensive and ongoing data collection related to volumetric analysis of kidney and liver images, evaluation of kidney blood flow, 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 Central Repositories (<http://www3.niddk.nih.gov/researchprograms/repositories/>) and are currently being used by outside investigators.

Finally, 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.

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National Institute of Neurological Disorders and Stroke (NINDS)

Senate Significant Items

Item

ALS. - The Committee is aware that basic research on ALS and a reservoir of pre-approved FDA drugs may provide the basis for drug development that could offer meaningful therapy for those with the disease. The Committee encourages NINDS to support clinical trials on ALS that are scientifically well-founded and have the opportunity to advance to “bedside” quickly. (p. 84)

Action taken or to be taken

NINDS funds basic research on amyotrophic lateral sclerosis (ALS) to identify the genetic determinants of ALS, define the molecular pathology, develop animal and cell-based model systems, and discover biomarkers (reliable biologic indicators that can be used to improve diagnosis and track disease progression). This research has led to the recent discovery of several new ALS genes, as well as a genetic modifier that slows the progression of the disease. The research has also resulted in the development of new biomarkers, including a method that measures muscle conductivity in ALS patients. Such biomarkers may soon be used in clinical trials as sensitive tools to measure the therapeutic effects of new treatments. NINDS is also supporting a consortium of researchers to derive induced pluripotent stem cells, a type of adult stem cell, from skin cells of ALS patients. These stem cells can be turned into motor neurons and other cells that are affected in the disease and have great potential as models for basic and translational ALS research. Each of these advances represents a critical step forward towards the development of new treatments for ALS.

NINDS has supported several clinical trials of drugs to treat ALS that were already approved by the FDA for the treatment of other diseases. These include clinical trials of minocycline, lithium carbonate and, most recently, ceftriaxone. Ceftriaxone, which is FDA-approved to treat bacterial infections, was identified as a potential ALS therapeutic through a NINDS-led drug screening program where a consortium of over 20 investigators collaborated to identify FDA-approved drugs with potential for treating neurodegenerative disorders. Laboratory studies conducted by this consortium suggested that the drug may also protect motor neurons from injury. Based upon these studies, NINDS funded a large double-blind, placebo-controlled clinical trial to determine whether ceftriaxone prolongs survival and slows disease progression in ALS patients. In July 2012, the trial was terminated early at the recommendation of the Data and Safety Monitoring Board because, based upon existing data, the study was unlikely to reach the pre-determined efficacy criteria. NINDS continues to explore the possibility that pre-approved FDA drugs may offer meaningful therapy for patients with ALS. To that end, NINDS currently supports investigator-initiated preclinical studies of guanabenz, which is FDA-approved to treat high blood pressure, and cyclosporine, which is an FDA-approved immunosuppressant.

In addition to re-purposing FDA-approved drugs, NINDS funds preclinical therapy development studies as well as clinical trials of novel drugs and cell-based therapies for ALS. In one study, researchers are developing high-throughput screening technologies and using them to identify novel drugs that may stop or slow the progression of ALS. NINDS-funded researchers are also

conducting preclinical translational studies to develop cell-based therapies for ALS. An NINDS-sponsored, early phase clinical trial to test the safety of transplanting cells into the upper spinal cord of ALS patients is currently under way.

Item

Dystonia. - The Committee recognizes the advancements that dystonia research has contributed towards an understanding of neuromuscular disorders and neurotrauma and encourages NINDS to continue to prioritize dystonia research. (p. 84)

Action taken or to be taken

The dystonias are movement disorders in which involuntary, sustained muscle contractions can affect a single muscle, a group of muscles (such as those in the arms, legs, or neck), or the entire body. NINDS will continue to place a high priority on research to improve our understanding of dystonia and to develop better treatments for the many types of dystonia. Dystonia research both benefits from and contributes to a broad spectrum of advances in biomedical research. Studies span many levels of analysis from genes, through molecular pathways, to the complex systems of brain cells that control movement.

In recent years, genetic discoveries have driven significant progress in dystonia research and that trend is continuing. Last year, for example, advances in technology enabled researchers to sequence the entire genomes (that is, all of the DNA) of a set of twins with a rare form of inherited dystonia. The insights from the whole genome sequencing immediately suggested a new therapeutic strategy that dramatically improved the twins' health. To date, research has identified more than 10 genes that, when defective, cause dystonia and investigators are closing in on several others. Researchers are building on the gene discoveries to understand how gene defects cause disease and to move toward therapies, for example by creating mice with the same gene defects and by developing laboratory tests for rapid screening of candidate drugs.

Another major line of research aims to improve deep brain stimulation (DBS), a therapy that uses surgically implanted brain stimulating electrodes to compensate for malfunctioning brain circuits. Clinical studies have confirmed long term benefits of DBS for people with some types of dystonia. DBS relevant research ranges from studies to better understand how the motor control circuits of the brain are disrupted in dystonia to investigations to optimize the technology and to determine where in the brain electrode placement is most effective. Studies of brain plasticity are among several other rapidly advancing areas of neuroscience research that contribute to our understanding of dystonia, including attention to non-genetic determinants of the disease.

Collaboration between medical researchers and patient advocacy groups through the Dystonia Coalition is a notable component of the NIH dystonia research program. NINDS and the Office of Rare Diseases Research (ORDR), within the National Center for Advancing Translational Sciences (NCATS), support the Coalition, as part of the ORDR Rare Diseases Clinical Research Network. This Coalition of researchers and patient advocacy groups is advancing the pace of translational and clinical research to find better treatments. Since it began in 2009, the Coalition has expanded to include more than 40 clinical sites and 13 patient advocacy groups.

Pharmaceutical companies also participate through the Coalition's annual meetings. Because several novel therapies for dystonia are advancing towards clinical testing, the Dystonia Medical Research Foundation, NIH, and others in the Coalition held a scientific workshop in May 2012 to consider the optimal design of clinical trials for dystonia.

NINDS is encouraged by the progress in dystonia research, driven by individual investigator initiated projects and by collaborative programs such as the Dystonia Coalition and continues to place a high priority on dystonia research.

Item

Epilepsy. - The Committee applauds the establishment and work of the Interagency Collaborative to Advance Research in Epilepsy, led by NINDS, as a means to focus Federal agencies and voluntary organizations on epilepsy research. The Committee also commends NINDS for announcing the next conference on curing epilepsy, to be held in March 2013, and for starting a new initiative to develop ways to manage epilepsy with no seizures and no therapeutic side effects. These new grants, the EUREKA grants and the Epilepsy Centers without Walls grants, are supporting creative and collaborative research that could lead to advances in prevention, diagnosis, or treatment of epilepsy and related co-morbidities. Additionally, the Committee commends NINDS for supporting the Partners Against Mortality in Epilepsy conference on sudden unexplained death in epilepsy. Finally, the Committee urges NINDS to heed the recommendations of the 2012 IOM report "Epilepsy Across the Spectrum: Promoting Health and Understanding". (p. 84)

Action taken or to be taken

NINDS is actively preparing to host the third Curing Epilepsy conference, to be held April 17-19, 2013, on the NIH campus, in partnership with patient and professional organizations. Two prior conferences in 2000 and 2007 led to the first and second sets of Epilepsy Research Benchmarks, which reflect the broad epilepsy community's goals to achieve no seizures, no side effects, and the prevention of epilepsy in those at risk. The 2013 conference will reunite the community to assess the current state of epilepsy research, and to identify emerging or unmet scientific opportunities and challenges for Benchmarks priorities over the next five to ten years.

NINDS held the third annual meeting of the Interagency Collaborative to Advance Research in Epilepsy (ICARE) on June 27, 2012. The meeting included sessions on comorbid conditions that affect people with epilepsy and post-traumatic epilepsy research within the Department of Veterans Affairs. In addition, participants heard a presentation on the Institute of Medicine (IOM) report, "Epilepsy Across the Spectrum: Promoting Health and Understanding," which reviewed public health dimensions of epilepsy and made recommendations in the areas of public health surveillance and data collection; population and public health research; health policy, health care, and human services; and education for people with epilepsy and their families, health care providers, and the public. Although direct consideration of biomedical research opportunities (such as those covered by the Epilepsy Research Benchmarks) was explicitly excluded from the report committee's charge, the report made recommendations for other types of health-related research within the missions of some ICARE member organizations. These recommendations were discussed at the ICARE meeting, with participants noting ongoing

efforts, opportunities, and challenges related to addressing identified opportunities. In particular, meeting participants discussed the recommendation to develop formal accreditation for epilepsy centers, which would meet specific criteria for epilepsy care and could also conduct clinical and health services research. Existing accredited centers for other diseases, such as stroke, were cited as potential models.

The IOM report is also a current focus of a HHS-wide epilepsy working group, on which NINDS serves, that regularly discusses approaches for implementing the report's recommendations. While many of these recommendations fall outside the purview of NIH, NINDS shares the report's overall vision for improving the lives of people with epilepsy and is working with the Centers for Disease Control and Prevention (CDC), other HHS operating divisions, and non-governmental organizations in areas where the report points to roles for NIH as a partner or source of expertise. For example, recommendations for improved surveillance and the prevention of epilepsy and its consequences include an emphasis on epilepsy-related mortality. In addition to funding research to better understand sudden unexplained death in epilepsy (SUDEP), NINDS provided funding and planning support for the first Partners against Mortality in Epilepsy (PAME) conference in June 2012. NINDS has also signed a Memorandum of Understanding with the National Heart, Lung, and Blood Institute to build on the CDC-led Sudden Unexpected Infant Death (SUID) Case Registry to create a registry of Sudden Death in the Young (SDY), including both SUDEP and sudden cardiac death (SCD). The SDY will be the first comprehensive surveillance system for SUDEP and SCD in the United States, and it will collect and store clinical information and biospecimens for research use.

Item

Headache Disorders. - The Committee encourages NINDS to put a higher priority on the causes of headache disorders as well as innovative treatments. (p. 84)

Action taken or to be taken

NIH recognizes the large public health burden of headache disorders and has taken steps in recent years to bring more attention to headache research among the research community and to identify gaps and opportunities to help move the field forward. The National Institute of Neurological Disorders and Stroke (NINDS) leads pain research efforts at NIH and Dr. Story Landis, NINDS Director, chairs the NIH Pain Consortium, which helps coordinate pain activities, including headache and related conditions, across NIH.

To encourage proposals in headache research and migraine headache, NIH has issued specific Funding Opportunity Announcements (FOAs), including "Migraine: Neural Mechanisms and Risk Factors for Progression" and the recently-renewed "Neurobiology of Migraine." These FOAs have successfully attracted and supported 15 new research grants in the past 5 years, including projects focused on causes of headache disorders and development of treatments. One of these projects, a whole genome association study to identify genes involved in migraine and their interaction with environmental factors, recently identified 3 genetic factors associated with migraine. Other projects funded by NINDS are aimed at understanding the role of genetic factors, hormones, and neuro-chemicals in headache susceptibility and progression. A NINDS Senator Jacob Javits Award in the Neurosciences (an award for highly meritorious research) was

recently presented to a headache researcher to explore the neural correlates and headache related symptoms associated with heightened sensitivity to light. NIH is working to expand the community of headache researchers and has increased its portfolio of new career development awards for headache research over recent years.

NIH is funding research to support development of pharmacological therapies for headaches, as well as behavioral therapies to prevent headaches. NINDS recently funded a pivotal comparative effectiveness trial of drugs to prevent pediatric migraine and to test the effectiveness of combined behavioral and pharmacological treatments for migraines in children. Animal model development for headache research is crucial for advancing drug development and NIH is funding research on new models based on different mechanisms implicated in headache. In addition, NIH-funded studies are being conducted to evaluate the efficacy of tailored behavioral strategies, massage, and lifestyle changes for migraine prevention. A number of these studies have been newly funded within the last couple years.

In addition to these efforts, NIH has been working with stakeholders to identify ways in which the field of headache research could be advanced further. The May 2010 “NIH Headache Research Planning Meeting” identified a number of key recommendations and NIH and NINDS have been responding to these, with the following activities: (i) holding a follow up scientific meeting to advance translational headache research; (ii) partnering with public and private entities such as the American Headache Society and the Food and Drug Administration to sponsor research symposia, conduct training sessions in grant writing for headache researchers at major scientific meetings, and develop improved analgesic drug trial design; (iii) funding Centers of Excellence in Pain Education to develop curriculum tools to train clinicians in pain treatment and management, with one Center targeted specifically for training in headache treatment; (iv) developing a set of common data elements for standardizing clinical research data from headache studies, in partnership with key players in the headache research community.

Item

Network for Excellence in Neuroscience Clinical Trials. - The Committee encourages NINDS to continue supporting the Network for Excellence in Neuroscience Clinical Trials [NeuroNEXT] program. The Committee urges NIH to increase the efficiency of clinical trials conducted through NeuroNext, facilitate patient recruitment and retention, and increase the quality of the neuroscience trials. The Committee also encourages NIH to work with other stakeholders to develop surrogate endpoints to more efficiently determine the success of a study. (p.84)

Action taken or to be taken

NINDS has launched the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) network and will expand its activities in the coming year. The network is explicitly designed to increase the speed, efficiency, and quality of early phase clinical trials for neurological disorders. As a multi-disease network, NeuroNEXT can keep resources and expertise more continuously engaged in productive research than would be possible in a single disease network. Through centralized resources, NeuroNEXT will enhance patient recruitment, efficiently handle regulatory and contractual issues, and rapidly engage appropriate teams of researchers and

clinical sites. NINDS is closely monitoring whether NeuroNEXT succeeds in improving the speed, costs, and quality of trials.

In 2011, NINDS established the NeuroNEXT central data and clinical coordinating centers and 25 clinical sites throughout the U.S. In May 2011, while development of the NeuroNEXT infrastructure was under way, NIH and FDA jointly sponsored a scientific workshop that brought together researchers and disease advocates to discuss the development of biomarkers for spinal muscular atrophy (SMA). Biomarkers, which include surrogate endpoints, are objective measures of the disease process or the biological actions of candidate therapeutics that can expedite therapy development. Based upon guidance from the workshop, NINDS solicited proposals for SMA biomarkers studies and funded SMA biomarkers clinical research as the first set of -clinical studies in NeuroNEXT in 2012. An important feature of NeuroNEXT is protection of intellectual property to encourage testing of the most promising candidate therapies, whether they arise from foundations, industry, or academia. In keeping with this goal, NINDS has solicited proposals for early phase clinical trials of interventions for neurological disorders from all of these potential sources and is now reviewing proposed clinical trials to be conducted by the network.

Item

Spinal Muscular Atrophy [SMA] Translational Research. - The Committee commends NINDS for supporting SMA therapy development projects through its Cooperative Program for Translational Research. This collaborative program has proven highly successful in accelerating the development of SMA therapies for testing in the clinic and facilitating the submittal of investigational new drug applications to the FDA. The Committee urges NINDS to use this approach as a model as it shifts its investment in SMA to the best opportunities based on current science, and to use the Cooperative Program for Translational Research to continue to advance and broaden the SMA drug pipeline. The Committee also applauds NINDS for its work on validating SMA biomarkers through the NeuroNEXT initiative. (p. 84)

Action taken or to be taken

NINDS is committed to accelerating the development of spinal muscular atrophy (SMA) therapies. Together with other parts of NIH, the Institute is pursuing the most promising opportunities for therapy development, whether via drugs, gene therapy, or biologic strategies. Ongoing projects in the NINDS Cooperative Program for Translational Research are focusing on small molecule drugs and on biologics, including therapeutic oligonucleotides. The program will also fund a major new SMA gene therapy project that builds on proof of concept results in mice and feasibility studies in non-human primates.

Other NIH programs also support SMA therapy development. For example, a collaboration between extramural researchers and the NIH Chemical Genomics Center, which is part of the NIH National Center for Advancing Translational Science (NCATS), developed a useful lead compound that increases cells' production of the SMN protein, whose deficiency causes SMA. In the realm of cell-based approaches, NIH has supported research to derive induced pluripotent stem cells from patients with SMA. The most immediate application is to rapidly screen potential drugs for SMA using cell culture methods, a strategy that is now under way in the

private sector. Other key investigations include the development of better small (mouse) and large (pig) animal models of SMA and, via the Eunice Kennedy Shriver National Institute of Child Health and Human Development, pilot testing of newborn screening methods that will facilitate early intervention, when therapies are most likely to have the strongest benefit. Of course, NIH continues to support basic research on SMA, which is the foundation of present and future progress. One basic project of note, for example, is identifying modifier genes for SMA, that is, genes that affect the severity of the disease caused by the primary gene defect. Modifier genes could reveal novel targets for therapy development.

Because novel therapies for SMA and several other neurological disorders are approaching readiness for clinical testing, NINDS developed the Network for Excellence in Neuroscience Clinical trials (NeuroNEXT), which is a multi-site clinical research network that will expedite early phase clinical testing of novel therapies. NeuroNEXT has established central clinical and data coordinating centers and 25 clinical sites, including Children's Hospitals, throughout the U.S. Following a joint NIH-FDA scientific workshop on SMA biomarkers that engaged the SMA research and patient community, and a subsequent solicitation for proposals, NINDS chose studies of SMA biomarkers as the first clinical investigations in the network. Biomarkers of disease progression or therapeutic action are key measures that will speed testing of therapeutic candidates. NINDS has also solicited proposals for NeuroNEXT clinical trials from academia, foundations, and industry.

Item

Stroke. - The Committee remains concerned that NIH spends only 1 percent of its budget on stroke research and strongly urges NINDS to expand its stroke portfolio. The Committee commends the leadership of NINDS in the decade-long work of the Stroke Progress Review Group and requests another status report, in the fiscal year 2014 congressional budget justification, on its Phase 2 stroke planning process to advance the most promising areas in prevention, treatment, and recovery research. (p. 85)

Action taken or to be taken

As the lead Institute for stroke at NIH, NINDS continues to make stroke a high priority, with stroke research representing over 10 percent of the Institute's budget. Stroke research at NIH is comprehensive and includes research to obtain a better understanding of basic disease mechanisms; epidemiological studies to assess stroke risk, occurrence and outcomes in the population; clinical research to develop effective prevention and acute treatment approaches; and development of strategies for improving recovery and rehabilitation in stroke patients. Clinical research in stroke in particular is a high priority at NINDS – approximately 50 percent of its large Phase III trials are on stroke.

Ten years ago, the Stroke Progress Review Group (SPRG) was asked to take a broad view in identifying and prioritizing unmet scientific opportunities that are critical to the advancement of the research field. The SPRG has provided NINDS and the research community with valuable guidance over the last decade. The most recent report, published in January of 2012, recognized 48 priority areas. Phase 2 of the stroke planning process was designed to build on the comprehensive analysis of the SPRG, identifying a smaller number of areas that represent the

most promising opportunities in stroke prevention, treatment, and recovery research. NINDS released a Request for Information (RFI) in May of 2012 to solicit broad input from the public and research community to identify opportunities for which significant, community-based effort and focus could lead to major advances in stroke research over the next five to ten years. Prior to the Stroke Research Priorities Meeting held August 29-30, 2012, members of three working groups—prevention, treatment, and recovery—rated over 180 RFI responses. Those pre-meeting scores were used to identify which proposals were discussed and further optimized for consideration as a top priority. By the end of the meeting, each workgroup had developed three top recommendations that represent in some cases modified and optimized versions of the best ideas presented in the RFI proposals. Recommendations from Phase 2 of the planning process were presented and discussed at the September 2012 meeting of the National Advisory Neurological Disorders and Stroke Council.

National Institute of Allergy and Infectious Diseases (NIAID)

Senate Significant Items

Item

Antibacterial Resistance. - The Committee applauds NIAID's decision to target antibiotic-resistant bacterial infections as the initial priority for the expansion of its clinical trials networks beyond HIV/AIDS. To further support research on antibacterial resistance, new antibacterial drugs, and new diagnostics, the Committee recommends that NIAID form a blue ribbon panel of experts including representatives from infectious diseases professional societies, the pharmaceutical and diagnostics industries, and others to create an antibacterial resistance strategic plan to assist in prioritizing research critical in this area. (p. 85)

Action taken or to be taken

NIAID pursues research to address antibiotic-resistant infections via investments in basic, translational, and clinical research. NIAID's goal is to shift the paradigm for antimicrobial drug development to focus on broad-spectrum therapies that could be used against entire classes of pathogens, thereby leveraging NIAID's investments in this area to achieve the greatest impact. NIAID works extensively with partners in industry, academia, and professional societies to develop research priorities and to support promising research in antimicrobial resistance.

Currently, NIAID participates in a number of expert panels to address the problem of antimicrobial resistance. NIAID co-chairs, along with CDC and FDA, the Federal Interagency Task Force on Antimicrobial Resistance. The Task Force developed and recently updated A *Public Health Action Plan to Combat Antimicrobial Resistance* with input from state and local health agencies, professional societies, pharmaceutical companies, consumer groups, and the public. The Task Force encourages feedback from external stakeholders, including via annual public meetings where progress on implementation of the Action Plan is discussed. NIAID also participates, along with HHS, CDC, FDA, and NIH, in the Transatlantic Task Force on Antimicrobial Resistance (TATFAR). TATFAR aims to enhance communication and cooperation in: antimicrobial stewardship; prevention and control of antimicrobial resistance; and research and regulatory strategies to enhance antimicrobial drug development. NIAID uses the recommendations of these expert panels, as well as input from a variety of stakeholders, to prioritize research on antimicrobial resistance and achieve maximum efficiency from the combined efforts of NIAID, professional societies, the pharmaceutical and diagnostics industries, and others. For this reason, NIAID does not plan to convene additional panels of experts to address antimicrobial resistance, and will continue to dedicate resources to productive partnerships with professional societies and industry to prioritize research and address this important issue.

NIAID has solicited input on a new endeavor to foster clinical research on antimicrobial resistance from scientific experts in professional societies, industry, and other organizations, including via town hall meetings and informal interactions. Taking these perspectives into account, in January 2012, NIAID released a Request for Applications to support a new leadership group for an antibacterial resistance clinical trial network. The antibacterial resistance

leadership group will develop and implement a comprehensive clinical research agenda to address the problem of antibacterial resistance. NIAID currently anticipates that an award for the leadership group will be made in 2014. This new program will also have an advisory component to help guide the research agenda.

NIAID will continue to offer tools and resources to the antimicrobial resistance research community to facilitate the highest-quality research and provide a flexible infrastructure to respond to emerging scientific opportunities; support basic and translational research likely to lead to clinical applications to reduce the prevalence of antimicrobial resistance; encourage development of broad-based vaccines and therapeutics effective against multiple pathogens; and facilitate the development of diagnostic tools that will enable clinicians to make informed treatment choices.

Item

Anti-Malarial Medications. - The Committee encourages NIAID to increase its support for public-private partnerships focused on developing anti-malarial medications and for research and development of alternatives to artemisinin combination therapies in response to the rapidly emerging threat of artemisinin resistance. (p. 85)

Action taken or to be taken

NIAID has long held a commitment to addressing the global health challenge of malaria through support of basic research and development of new diagnostics, treatments, and vaccines for malaria. Public-private partnerships among NIAID, governmental and non-governmental organizations, academic institutions, and industry will play a crucial role in translating basic scientific discoveries in malarial biology into new anti-malarial therapies.

Public-private research collaborations supported by NIAID have demonstrated progress in the development of new anti-malarial medicines. With NIAID support, an academic researcher affiliated with a major pharmaceutical company is investigating a new class of drugs with a novel anti-malarial mechanism—the spiroindolones. One member of this drug class has been shown to rid mice of malaria parasites after a single oral dose. Further tests are planned to inform whether the pharmaceutical company will continue development of this spiroindolone. NIAID also has participated in a successful joint effort with the public-private Medicines for Malaria Venture. The partnership has characterized dihydroorotate dehydrogenase, a promising target for anti-malarial therapies, and identified a candidate drug for further study and product development.

The NIAID intramural research program also works to address the problem of anti-malarial drug resistance via domestic and international partnerships. NIAID investigators are working with scientists in Africa and Southeast Asia to define the response to artemisinin in areas where artemisinin combination therapies are first-line treatments against malaria. This project could be a model to inform efforts to counter artemisinin resistance and improve malaria treatment worldwide. Recently, NIAID teamed with the Fogarty International Center to convene *Artemisinin Resistant Malaria: Research Challenges, Opportunities, and Public Health Implications*, a meeting of diverse stakeholders to address the growing challenge of resistance to

artemisinin combination therapies. A review of the meeting's findings on artemisinin resistance, approaches for translating research data into relevant public health information, and opportunities for interdisciplinary collaboration to combat artemisinin resistance was published in the *American Journal of Tropical Medicine and Hygiene* in August 2012.

NIAID scientists also work with a variety of partners to search for new anti-malarial drugs, 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 investigators in partnership with the Medicines for Malaria Venture has identified chemicals that kill malaria parasites by blocking a key pathway for nutrient uptake. These compounds will be further investigated as candidate anti-malarial medicines. Similar NIAID research partnerships will continue to investigate the development of new and improved anti-malarial medicines. NIAID will continue to address the global challenge of malaria via these efforts, as well as through research on malaria control strategies and the development of malaria vaccines.

Item

Food Allergies. - The Committee is pleased with the support and clinical advancement of promising food allergy research at NIAID and NIDDK. NIH is currently evaluating potential immunotherapy protocols for clinical implementation in children and adults with food allergy. The Committee encourages NIAID to continue its public-private partnerships in support of clinical immunological, immunomodulator, and mechanistic studies, with private donors and foundations as components of ongoing clinical trials. (p. 85)

Action taken or to be taken

Between 2003 and 2012, NIAID increased its funding of food allergy research from \$1.2 million to \$25.3 million. As part of this effort, NIAID and NIDDK sponsor the Consortium of Food Allergy Research (CoFAR). In collaboration with private organizations, CoFAR is developing new immunotherapeutic approaches, including oral immunotherapy (OIT), to treat food allergy and prevent food allergy-associated anaphylaxis. A recent CoFAR study demonstrated that egg OIT is safe and effective in egg-allergic children, 5 to 18 years old. The majority of study participants could be safely desensitized while on maintenance OIT and approximately one in four (of this majority) was able to eat egg even after stopping OIT for four to six weeks. These same children could consume dietary egg without allergic reactions for at least one year. Another recently published CoFAR study suggests that sublingual immunotherapy can reduce the allergic response to peanut in adolescents and adults. Additional CoFAR studies are examining similar OIT and other immunotherapy approaches for treatment of egg and peanut allergy in various populations.

The NIAID Immune Tolerance Network (ITN) and the Asthma and Allergic Diseases Cooperative Research Centers (AADCRCs) are conducting other clinical trials of OIT. These include a trial of peanut OIT in very young children with peanut allergy; another trial of the safety and efficacy of peanut OIT in adolescents and adults with peanut allergy; a trial to determine whether oral peanut consumption initiated at ages four to ten months, in children at risk of developing peanut allergy, will prevent the development of peanut allergy by age five; and a trial using milk OIT with omalizumab (anti-IgE) or baked cow's milk OIT to treat cow's

milk allergy. Many of these NIAID-supported clinical trials are accompanied by mechanistic studies aimed at developing a better understanding of the factors that underlie the development or natural resolution of food allergy and/or response to therapy. Such studies will be critical in the further development of successful approaches to prevent and treat food allergy. The NIAID AADCRCs will be recompleted in FY 2013 and the ITN in FY 2014.

NIAID continues to consider new partnerships with biotechnology and pharmaceutical companies, private organizations, and foundations to conduct clinical trials for treatment or prevention of food allergy. Though OIT remains the most promising approach for treating and preventing food allergies, it is currently an experimental therapy whose safety and efficacy must be replicated in larger clinical trials.

Item

Hepatitis B. - The Committee is pleased with the emergence of new and improved drugs to treat hepatitis B and the role that NIAID continues to play in this effort. However, drugs are effective in only half of the population, and for those patients that can take these medications there is still only a 50 percent reduction in mortality over a 10-year period. The Committee urges a more aggressive effort in this area. (p. 85)

Action taken or to be taken

Hepatitis B virus (HBV) is responsible for the majority of the worldwide hepatitis burden, and in the United States, chronic hepatitis B-related cirrhosis and liver cancer cause more than 3,000 deaths each year. NIAID pursues research to understand the biology of HBV infection and to develop new classes of drugs to treat HBV infections. NIAID supports a number of research grants to conduct basic research and to develop novel therapies for HBV. NIAID-supported researchers are pursuing the early-stage development of therapies targeting the HBV surface antigen, viral capsid, HBV covalently closed circular DNA (cccDNA), as well as the host's innate immune system.

NIAID investigators are working closely with pharmaceutical companies in clinical studies of improved HBV therapeutics. For example, NIAID scientists are partnering with industry to test the safety, antiviral efficacy, and tolerability of the oral drug GS-7340 in chronic HBV patients in Washington, D.C. In another collaboration, a NIAID outpatient clinic participates in a multicenter study of GS-9620, a novel drug for treatment of chronic HBV. In addition, NIAID scientists are collaborating in laboratory studies to characterize a promising vaccine candidate that targets three HBV antigens. The goal of this project is to pursue clinical trials of this candidate as a therapeutic HBV vaccine.

In recent years, NIAID has 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. In FY 2012, 250 compounds were screened for antiviral activity against HBV.

Candidate HBV drugs, as well as new therapies to help the immune system fight HBV infection, are screened and evaluated through contracts supported by NIAID using animal models. Animal models for HBV infection supported by NIAID 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 to identify new HBV drug targets and test new therapeutic strategies to treat HBV infection.

Through investments in basic, translational, and clinical research, NIAID will continue to support its diverse research program on HBV, with emphasis on the development of novel therapies to combat HBV infection.

Item

Microbicides. - The Committee encourages NIAID to continue coordination with USAID, the State Department, and others to advance antiretroviral [ARV]-based microbicide development efforts, with the goals of enabling regulatory approval of the first safe and effective microbicide for women and supporting product development and efficacy trials of alternative ARV-based microbicides. (p. 85)

Action taken or to be taken

NIAID continues its longstanding effort to identify safe and effective interventions, including microbicides, to prevent HIV infection. NIAID coordinates with a variety of partners to advance the development of microbicides, including the U.S. Agency for International Development (USAID) and the Department of State, the Centers for Disease Control and Prevention (CDC), the International Partnership for Microbicides (IPM), the Center for AIDS Programme of Research in South Africa (CAPRISA), CONRAD, and the Bill and Melinda Gates Foundation (BMGF).

The NIH Office of AIDS Research (OAR) in the NIH Office of the Director facilitates collaboration among all of the NIH Institutes and Centers that support microbicides research and plans and coordinates microbicide research activities across the Federal government through a number of activities. For example, OAR convenes and chairs the Trans-NIH Microbicide Research Coordinating Committee, which develops the annual Trans-NIH Plan for HIV-Related Research outlining the strategic plan for microbicides and establishing trans-NIH research priorities. OAR also established and chairs a Trans-Governmental Microbicide Coordinating committee, comprised of NIH Institutes and Centers (IC), CDC, the U.S. Food and Drug Administration (FDA), the Departments of Defense and Veterans Affairs, and USAID, to facilitate further coordination and collaboration in this area. OAR established the Microbicides Research Working Group (MRWG), an independent non-governmental panel of experts that advises NIH and other entities supporting microbicide research and development. Relevant NIH ICs, including NIAID, as well as CDC, FDA, USAID, and non-governmental organizations including CONRAD, the Population Council, IPM, BMGF, and international organizations are invited to attend meetings and to submit issues and topics to the MRWG for consideration. OAR

also convenes meetings of the microbicides research funders to encourage consensus on the future funding goals for microbicides research.

NIAID also helps to facilitate future product regulatory approval of microbicides by providing support for basic research through preclinical development and clinical trials. In 2010, with NIAID and other NIH infrastructure support, the CAPRISA 004 trial 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 and MTN-007, two Phase I studies indicating that tenofovir gel was safe and 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 drug concentration in the vagina than did the oral tablet. NIAID also supports the Comprehensive Resources for HIV Microbicide and Biomedical Prevention contract, which assists academic investigators and pharmaceutical companies by performing pharmacology and toxicology studies to enable clinical testing of microbicides candidates.

NIAID supports microbicide clinical studies as the primary funder of the Microbicides Trials Network, which is co-funded by NICHD and NIMH. The MTN also collaborates with USAID, IPM, and CONRAD as well as other microbicide sponsors and donors to test the most promising microbicides for safety and effectiveness. For example, in 2012, the MTN implemented a novel Phase III safety and effectiveness study of the antiretroviral drug dapivirine delivered in a vaginal ring in collaboration with IPM, BMGF, and Tibotec, a component of Janssen Pharmaceutical Companies. This study is among the first to evaluate an approach using a vaginal ring to provide sustained delivery of a potent ARV-based microbicide. Through the MTN, NIAID also supported the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study, or MTN-003. VOICE was a Phase IIb microbicide study designed to evaluate oral and topical ARV-based approaches to prevent HIV transmission in women. The study results indicated that the three antiretroviral-based strategies intended to prevent HIV infection among women did not prove effective. For reasons that are currently unclear, a majority of study participants were unable to use their assigned approaches daily as directed. VOICE C and VOICE D sub-studies are exploring women's motivations for adherence or non-adherence and hope to be able to further elucidate the issues that influenced their decisions in the study. The primary study results were announced at the Conference on Retroviruses and Opportunistic Infections (CROI) in March 2013.

NIH will continue to support microbicide research by evaluating additional products for use as vaginal and rectal microbicides in a variety of populations, determining the best predictors of microbicide safety and efficacy, developing microbicide formulations that are easy to use, and investigating the best methods to deliver the drug.

Item

Neglected Tropical Diseases [NTDs]. - The Committee urges NIAID to continue its investment in neglected tropical disease and malaria research, including translational research for NTDs, and to work with other agencies as a part of the Global Health Initiative to foster research and ensure that basic discoveries are translated into solutions. (p. 85-86)

Action taken or to be taken

NIAID has for many years pursued a program of research devoted to better understanding, treating, and preventing neglected tropical diseases (NTDs). NIAID's program on malaria and NTDs includes support for basic research on the biology of NTD infections as well as translational research to facilitate development of new tools and interventions against NTDs. NIAID partners with other U.S. government agencies, industry, and non-profit organizations in NTD research endeavors and supports the goals of the President's Global Health Initiative to reduce the prevalence of seven NTDs by 50 percent, contributing to the elimination of leprosy and onchocerciasis in Latin America by 2016, and lymphatic filariasis by 2017.

In the last several years, NIAID has built upon existing international efforts by expanding research efforts in malaria and NTD-endemic countries. In 2012, NIAID funded eight Tropical Research Medicine Centers (TMRCs) to support research on NTDs in endemic areas throughout the world, including the Philippines, Brazil, India, Thailand, Mali, Ghana, and Peru. NIAID supports ten International Centers of Excellence for Malaria Research (ICEMR) awards designed to conduct multi-disciplinary research on malaria in all malaria-endemic regions of the globe. In addition to ongoing work at these centers, NIAID has made awards under the *Development of Novel Interventions and Tools for the Control of Malaria, Neglected Tropical Diseases and their Vectors* initiative to support early translational research exploring novel vaccines, diagnostics, and vector management strategies for malaria and NTDs. NIAID also made new awards under the *NIAID Partnerships with Product Development Public-Private Partnerships* program to facilitate later-stage preclinical and translational research for NTDs, including Chagas' disease, schistosomiasis, and African trypanosomiasis. In addition, NIAID has supported research to investigate antiviral drugs against dengue virus, screening 12,761 compounds against dengue virus type 2 and identifying 53 compounds for further evaluation since 2004. NIAID supports antigen discovery, early-stage vaccine identification, and evaluation of NTD and malaria vaccine candidates, including eight malaria candidate vaccines in clinical trials and recombinant vaccines against *Schistosoma mansoni* and lymphatic filariasis. NIAID also supported pre-clinical development activities for a visceral leishmaniasis vaccine that entered a Phase I clinical trial in 2012.

NIAID intramural researchers are studying NTDs such as lymphatic filariasis and leishmaniasis in U.S.-based laboratories and through NIAID's International Centers for Excellence in Research in India and Mali. Conducted in collaboration with government agencies, this research strives to promote infrastructure development and research training and to improve the diagnosis and treatment of these diseases. This successful research effort has produced widely used diagnostic tools for filariasis and leishmania infections. NIAID scientists also have built upon a longstanding research program in basic and applied arbovirus research with the development of a dengue virus vaccine currently in clinical trials in the United States. Additional candidate vaccines for dengue are in various stages of development with support from NIAID.

NIAID will continue its support for basic and translational research to facilitate greater understanding of the biology and effective treatment of malaria and NTDs. NIAID remains committed to conducting and fostering research to develop new diagnostics, treatments, and vaccines for these important diseases. Partnerships between NIAID, other governmental and

non-governmental organizations, and private industry will play a crucial role in translating key scientific discoveries into solutions for malaria and NTDs.

Item

Nontuberculous Mycobacterial [NTM] Disease. - The Committee urges NIAID to intensify research into NTM infections so that more effective interventions can be developed for patients. (p. 86)

Action taken or to be taken

A better understanding of the biology of nontuberculous mycobacteria (NTM) infections will be critical to developing more effective interventions for patients, including drugs, vaccines and diagnostics for NTM infections. NIAID currently supports a number of research grants on NTMs including basic research to understand better the epidemiology and pathogenesis of NTMs as well as research that could lead to candidate diagnostics and treatments.

NIAID intramural researchers have led efforts to understand the epidemiology, pathogenesis, and treatment of NTM infections. In a national study of non-HIV infected populations, NIAID researchers have found that NTM infections are an increasing cause of illness in the United States, particularly among women in certain geographic areas. The researchers also have discovered that susceptibility to pulmonary NTM infection is likely inherited. Following up on these insights, NIAID scientists are currently designing clinical trials of inhaled drugs to treat pulmonary NTM infections.

NIAID's longstanding research efforts on tuberculosis have contributed greatly to the resources available for research on NTMs. For example, NIAID's contract for Tuberculosis Research Materials and Vaccine Testing prepares research reagents useful for NTM research. NIAID tuberculosis drug development resources also include opportunities for testing candidate drugs and compounds against NTMs to identify early drug leads. In the future, NIAID plans to expand other existing tuberculosis-specific research resources to include NTMs. Additionally, NTM researchers can access the preclinical and clinical research resources and services NIAID provides to facilitate the translation of products from bench to bedside, including *in vitro* testing of potential drug compounds for efficacy against a diverse set of NTM isolates as well as *in vivo* testing in a mouse model.

To facilitate collaboration and dissemination of research on NTMs, NIAID will continue to support a workshop, *Many Hosts of Mycobacteria*, to discuss critical issues in comparative mycobacteriology. This workshop will help to identify similarities, differences, critical points of intervention, research reagents, and product development needs for mycobacterial infections of livestock and of humans.

A solid understanding of the pathology and physiology of disease-causing mycobacteria will be critical to defining clinically useful drugs, vaccines and diagnostics for mycobacterial diseases. NIAID is committed to supporting research that may lead to more effective preventive and therapeutic approaches for NTM infections.

Item

Specimen Collection. - Collecting specimens is critical to research and development of diagnostic tests or other activities intended to advance the treatment, detection, identification, prevention, or control of antimicrobial-resistant infections. The Committee urges NIAID, in conjunction with CDC, ASPR, and the FDA, to consult with representatives from diagnostics and pharmaceutical companies, academia, and professional societies to explore the most effective way to provide samples, including the feasibility of creating a biorepository of prospectively collected specimens. (p. 86)

Action taken or to be taken

Cells, tissues, and organisms are the building blocks of basic research, including research on antimicrobial-resistant infections. NIAID provides access to existing repositories of material that can be utilized by the general scientific community through the BEI Resources Repository, which has a collection of hundreds of specimens. The NIAID intramural program also provides access to antimicrobial-resistant organisms isolated from clinical samples through scientific collaborations and material transfer agreements. Such existing mechanisms allow sharing of critical resources with scientists from academia and the private sector.

NIAID agrees that specimen collection for diagnostic and therapeutic development is critical to the field. The needs of researchers and product developers for specimens are often very specific. This poses a challenge for the prospective collection of specimens, before the full characteristics of each specimen have been investigated. In the Institute's experience, the most successful and efficient specimen collection strategies are those conducted in response to a specific request, rather than a broad repository that requires extensive resources to maintain. This specific request model, whereby specimens would be collected after *bona fide* need has been demonstrated, would avoid storage of specimens that may never be used, or that may not be preserved in the manner required by a future research protocol. NIAID has consulted on this matter with stakeholders in the community, and is aware that a number of companies are developing collections containing a broad variety of specimens, but which are specifically designed for research on antimicrobial resistance as well as the development of diagnostics and therapeutics.

In January 2012, NIAID released a Request for Applications to support a new Leadership Group for a Clinical Research Network on Antibacterial Resistance similar to the existing HIV/AIDS clinical research networks (<http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-12-019.html>). The Leadership Group will develop and implement a comprehensive clinical research agenda to address the pressing problem of antibacterial resistance. The Leadership Group will have the capacity to collect specimens for research on antibacterial resistance in response to specific requests consistent with its comprehensive clinical research agenda.

NIAID will continue to work with stakeholders, including the CDC, ASPR, FDA, and representatives from diagnostics and pharmaceutical companies, academia, and professional societies to address the issue of finding the most effective way to provide specimens, as well as to make sure that existing resources are well used.

Item

TB. - The Committee strongly urges NIAID to expand its research into the development of new TB diagnostic tests, drugs, and vaccines, particularly regarding drug-resistant TB and totally drug-resistant TB. (p. 86)

Action taken or to be taken

Tuberculosis (TB) remains a significant global public health challenge, the magnitude of which is intensified by the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) forms of TB as well as the increasing incidence of TB/HIV co-infection. To address this challenge, NIAID pursues research on tools to prevent, diagnose, treat, and control TB. The objectives of NIAID's TB research program are to fill critical gaps in product development; to identify and advance drugs with novel modes of action; to improve regimens using new and existing drugs that will shorten the duration of TB therapy; and to identify effective vaccines that will lead to long-lasting protection against all forms of TB, including TB in HIV-infected populations.

A recent notable success in the fight against TB is a new diagnostic—Cepheid's Gene Xpert MTB/RIF assay—developed with NIAID support. This rapid test, endorsed for widespread use by the World Health Organization, will accelerate diagnosis of TB throughout the globe and can help to determine optimal treatment by rapid identification of drug-resistant TB. NIAID is working to expand use of the test to identify XDR TB within public health settings and develop additional easy-to-use diagnostic tools appropriate for a number of settings and a variety of clinical samples.

NIAID's investments in basic science have contributed to a number of additional TB diagnostics and drugs in clinical development. Currently, NIAID is evaluating an assay to diagnose TB and detect drug resistance in HIV patients. NIAID *in vitro* and *in vivo* preclinical and clinical support contracts have contributed to the advancement of several clinical candidate TB drugs. These include two drugs originally developed by NIAID intramural scientists, SQ109 by Sequella Inc. and PA-824 by the Global Alliance for TB Drug Development. NIAID is also supporting early-stage clinical trials of experimental TB drugs, including AZD5847 in adult TB patients, TMC 207 administered with an antiretroviral drug, and a Phase II clinical trial of high dose isoniazid for treatment of different genetic variants of MDR TB.

NIAID has supported the development of approximately ten TB vaccine candidates. Currently, NIAID funds collaborative clinical studies with AERAS to evaluate prophylactic TB vaccines, including a Phase II safety and efficacy trial of an adenovirus-based booster following priming at birth with the current TB vaccine, BCG, in HIV-negative infants. 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.

In addition, NIAID researchers collaborate with international investigators on several studies of drug-resistant TB and clinical trials of novel TB treatments. NIAID has developed critical collaborations in South Korea to pursue clinical studies of two drugs repurposed for use against drug-resistant TB, recently finding that linezolid is efficacious for the treatment of previously

untreatable XDR TB. A partnership with the Korean Ministry of Health and Welfare is developing new rapid diagnostics for MDR and XDR TB, performing clinical studies of metronidazole and linezolid to treat drug-resistant TB, and developing a protocol to shorten the length of treatment for MDR and XDR TB.

NIAID's sustained investment in research from basic biological understanding of TB through clinical development of TB interventions will lead to improved diagnostics, drugs, vaccines, and intervention strategies for combating TB, including MDR and XDR TB.

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National Institute of General Medical Sciences (NIGMS)

Senate Significant Items

Item

Institutional Development Awards [IDeA]. - The Committee provides \$276,480,000 to continue increased support for the IDeA program. The Committee recognizes the importance of the Centers of Biomedical Research Excellence [COBRE] and the IDeA Networks of Biomedical Research Excellence [INBRE] programs. The Committee believes the IDeA program has made a significant contribution to biomedical research and creating a skilled workforce. Therefore, the Committee continues the \$45,882,000 increase from fiscal year 2012 and recommends that one-half the increase go toward new COBRE awards. The increase should be paid for by a reduction in funding across NIH ICs. The Committee encourages the NIH Director to expand the program to support co-funding 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. Therefore, the Committee directs the IDeA Director to expand IDeA eligibility to all NSF EPSCoR-eligible States. (p. 86-87)

Action taken or to be taken

In fiscal year 2012, NIH received an additional \$45,882,000 for support of a new COBRE competition and new awards for the IDeA Clinical and Translational Research Program (IDeA-CTR). As a result, nine new COBRE awards were made and support was provided for 4 COBRE competing continuation (Phase II) awards and 12 new COBRE Phase III awards. Twenty-two R01 awards were co-funded across 17 NIH Institutes and Centers. Support for ongoing non-competing COBRE and INBRE awards continued.

Plans for FY 2013 under the President's Budget request include continued support for the non-competing COBRE and INBRE awards that constitute the IDeA base. Continued support of Research Project (R01) awards solicited from across the NIH Institutes and Centers for co-funding as well as new awards in FY 2013. Support will be provided for new Phase I COBRE awards as well as for Phase II and Phase III COBRE awards. Two INBRE awards will compete for continued support. NIH will continue to support IDeA-CTR awards based on availability of funding.

Eligibility to compete for IDeA funds has been outlined in law through the Public Health Service Act, Title IV, Part C, Subpart 11, Section 461(b) (as amended by the Consolidated Appropriations Act (P.L. 112-74, 12/23/2011)) and is based on two criteria, an institution's grant success rate and its total NIH funding. Eligibility criteria is defined in Section 461(b)(1)(B), which states, in part, that: "*entities that conduct biomedical and behavioral research and are located in a State in which the aggregate success rate for applications to the national research institutes for assistance for such research by the entities in the State has historically constituted*

a low success rate of obtaining such funds, relative to such aggregate rate for such entities in other States". In order to change this criteria, statutory language would be required.

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

Item

Children in Military Families. - Given that nearly 2 million children live in military families and 700,000 children have been affected by a recent or current deployment of a parent, the Committee commends NICHD for supporting research on the impact of these experiences on child health and well-being and on the effectiveness of programs designed to address the psychosocial and mental health needs of children and their families. Studies are needed to examine the unique developmental challenges of children when the mother or female head of household is deployed to a combat zone, the process of adjustment when military personnel return home, and the long-term consequences of separation and reintegration on children's development. (p. 87)

Action taken or to be taken

The cycle of deployments and reintegration within the family are known to be stressful events in the life of a military family. For children and adolescents especially, parental deployment may be even more unsettling. Studies supported by NICHD examine the long term impact of deployment on the developmental trajectories of children in military families and test interventions developed to support healthy family functioning.

In an ongoing study, NICHD-supported researchers focused specifically on children aged 6-12 whose parents were deployed. The study, uniquely focused on children's behavior and emotional functioning, showed that a parent's combat deployment has an adverse effect on children, which increases the longer the parent is away. Notably, these effects remain even after the parent returns home. Nearly one-third of the children whose parents are deployed reported "clinically significant" levels of anxiety, whether or not the parent had returned from deployment. The children's high levels of anxiety coincided with high levels of anxiety and distress in the parent who stayed at home. Moreover, nearly a quarter of the enlisted parents tested positive for post-traumatic stress disorder after returning from deployment, further complicating family situations.

The impact of deployment on the service member, coupled with distress and emotional symptoms in the non-deployed parent, places military families at particular risk, and this is most pronounced for families in the National Guard and Reserves. Another NICHD-funded project aims to address the needs of military families with young children (2- to 5-years-old) following a deployment, with a particular focus on the Guard and Reserves. This is group-based parenting intervention for service members, their partners, and children aimed at enhancing positive parenting through an intervention that incorporates five core pillars: 1) parent education, 2) social support, 3) supporting parent-child interactions, 4) connecting families to resources, and 5) improving stress reduction and self-care skills.

A new NICHD-funded Small Business Innovation Research Grant is also developing innovative ways to strengthen family functioning and improve child outcomes in military families following deployment. Partnering with the Departments of Veterans Affairs and Defense and academic

institutions, the grant will allow a small business to develop, evaluate, and disseminate After Deployment: Adaptive Parenting Tools (ADAPT). Based on research on cognitive skills and the regulation of emotion, ADAPT will be an online, interactive resource for military parents; targeting veteran families who are at risk for depression, anxiety, substance abuse, mental illness, and post-traumatic stress, among other conditions. In addition to special training for military parents, ADAPT will provide useful information to therapists and organizations serving military families.

NICHD also supports research on potential differential affects on individuals from disadvantaged backgrounds after being discharged from military service. This project estimates the causal effects of service in the U.S. military, America's largest employer of young high school graduates, on labor market outcomes to better understand the consequences of early labor market experiences of low-aptitude youth; with a special focus on low-income and minority youth.

Item

Chromosome Abnormalities. - The Committee continues to support additional research on chromosome abnormalities and urges NICHD to consider holding a state of the science meeting focusing on strategies aimed at devising treatments for recurring and nonrecurring copy number changes. The Committee further urges new funding to support other independent investigators whose work can provide pilot data or insight into future directions for the study of more chromosome abnormalities, particularly those involving chromosome 18. The Committee requests an update on these activities, focusing on non-Down syndrome research, in the fiscal year 2014 congressional budget justification. (p. 87)

Action taken or to be taken

NICHD continues to support studies that identify critical genes within regions that contain chromosomal abnormalities. Greater emphasis is now being placed on application of DNA-based technologies (e.g., cytogenomic arrays) that identify small chromosomal regions, known as Copy Number Variants (CNVs). CNVs are likely to account for 20 percent of unexplained developmental delays, intellectual disabilities, autism spectrum disorders, and multiple birth defects. NICHD-funded investigators contribute to the creation, implementation, and dissemination of a comprehensive atlas of CNVs through the International Standards for Cytogenomic Arrays (ISCA) Consortium. Established in 2007, the ISCA Consortium has membership that includes over 160 institutions worldwide, with over 1,200 registered individual members. The Consortium has collected data on almost 30,000 cases of chromosomal abnormalities detected by CNV analysis with corresponding clinical information, which is deposited in a publicly available database. This rich dataset serves as a reference to understand better the effects of extra or missing chromosomal material on an individual and his/her development, thus allowing clinicians and researchers to share knowledge about critical genes within CNVs in defined populations, such as those with intellectual disabilities. The ISCA Consortium hosts an annual conference to update members about CNV standards, phenotypic data collection, and outreach to the community; NICHD representatives attended the most recent conference held in May 2012, where participants discussed the goal of expanding this resource to encompass all clinically meaningful genomic variants as a tool to understand human disease.

NICHD continues to support research regarding duplications and deletions of chromosomal material that include contiguous genes on critical chromosomes like 18 and 21, which are associated with developmental delay and malformations. Further, NICHD also supports numerous investigator-initiated research studies that focus on contiguous gene disorders located on other chromosomes (e.g., Angelman syndrome, Prader-Willi syndrome, and duplication 15q11-13 syndrome (all on chromosome 15); Smith-Magenis syndrome and Potocki-Lupski syndrome (chromosome 17); Williams syndrome and duplication 7q11 syndrome (chromosome 7); and DiGeorge syndrome or velo-cardio facial syndrome (chromosome 22)). NICHD supports a Rare Disease Clinical Research center based at the University of Alabama, Birmingham, which focuses on Rare Epigenetic Disorders (e.g., Angelman, Rett, and Prader-Willi syndromes) to better understand the extent of associated intellectual and developmental disabilities in these conditions. This center has numerous sites throughout the U.S. that conduct longitudinal natural history studies, examine the abnormal sleep patterns that commonly occur, and conduct pilot clinical studies to improve outcomes and evaluate interventions for these disorders. For example, in a recent study, scientists showed that children with Angelman syndrome exhibited alterations in white matter pathways of the brain compared with typically developing children, and some of these alterations were associated with severity of their Angelman symptoms in language, cognitive, and social functioning. Collectively, insights gained from these studies will provide a knowledge base to inform the development of new diagnostics and therapeutics for individuals with rare genetic diseases and chromosome abnormalities.

Item

Demographic Research. - The Committee commends NICHD for supporting large-scale databases, such as the National Longitudinal Survey of Youth, the Child Development Supplement of the Panel Study of Income Dynamics, and the Fragile Families and Child Well-Being Study, and demographic research activities, such as the Population Research Infrastructure Program. These investments have generated key scientific findings, illuminating in particular the relationship between socioeconomic status and individuals' health and well-being. As NICHD implements its ambitious reorganization and scientific visioning process in fiscal year 2013, the Committee urges the Institute to continue its commitment to supporting demography and population science. (p. 87)

Action taken or to be taken

NICHD continues its longstanding support of its Population Infrastructure Research Program, and of longitudinal population studies that yield data widely used by the scientific community to inform our understanding of human populations and health, demographic change, and behavioral and social science.

For example, new results from the National Longitudinal Study of Adolescent Health (“Add Health”) contribute to the growing body of evidence highlighting the potential risks of being overweight during pregnancy. Add Health is one of the only data resources that allow scientists to examine how a woman’s health and behaviors, prior to conception, can affect her baby’s health. Researchers using Add Health data found that women who are overweight or obese during the transition from adolescence to adulthood are more likely to deliver babies with higher birth weights, resulting in increased likelihood that the next generation of children will become

obese and the potential for obesity-related health risks. Other researchers using these data showed that even when socioeconomic factors are considered, young adults with healthy parents are more likely to graduate from high school and complete college than young adults with unhealthy parents. This finding suggests that improvement in parental health may improve their children's educational outcomes.

The NICHD-funded Study of Early Child Care and Youth Development provides a wide range of useful information to help families deal with common day-to-day challenges faced by families in the United States. One research team using these data found that mothers who work during their children's infancy and preschool years tend to be healthier and happier than mothers who stay at home, with no differences reported between mothers who worked full-time and those who worked part-time. Another analysis, found that mothers who placed their children in high quality day care as infants were more likely to be involved in their children's schools after they entered kindergarten, including maintaining regular contact with teachers.

Based on recent scientific "visioning" activities within NICHD, the Demographic and Behavioral Sciences Branch will be renamed the Population Dynamics Branch. This change will better highlight the breadth of the Institute's work supported in the area of population studies and demographic change. NICHD remains committed to investing in longitudinal studies that can provide unique insight into the many factors that can affect children's development and health and well-being throughout life.

Item

Kidneys and Childhood Development. - The Committee urges NICHD, in consultation with NIDDK, to undertake efforts to examine the role of normal kidney development and/or function in neonatal and child health. Specific areas to be addressed should include: kidney function in low-birth weight infants; how chronic acidosis, untreated hypertension, or recurrent urinary tract infections affect child development; the impact of childhood-onset hypertension on adult cardiovascular health; and the identification of genetic and epigenetic factors that may subsequently result in kidney injury and progression of hypertension and chronic kidney disease. (p. 87-88)

Action taken or to be taken

NICHD supports research on normal kidney development and/or function in neonatal and child health, including on the developing fetal kidney and risk of hypertension later in life. For example, the Institute is currently funding a large research project on determining the effect of administration of antenatal steroids on the developing kidney and on the development of later hypertension. Currently, widespread use of antenatal steroids has significantly reduced infant mortality in premature babies, but concerns have been raised about potential risks posed by this practice. Using animal models, NICHD-supported investigators have demonstrated that exposure to antenatal steroids *in utero* results in permanent changes in the young animals that persist later in life and lead to hypertension. The same investigators have conducted complementary human studies, which show that early adolescents, who were exposed to antenatal steroids *in utero*, exhibit higher systolic blood pressure, a harbinger for hypertension in later life. These research findings have important health implications, indicating that individuals

treated with antenatal steroids may be at higher risk for poor health outcomes and need to be followed to minimize the development of hypertension.

NICHD also is supporting a range of research projects on maternal nutrient deprivation (MND), both on fetal development and the onset of adult disease. Under-nutrition during pregnancy causes intrauterine growth restriction, and these infants have smaller kidneys containing fewer nephrons—the basic functioning unit in the kidney. Such infants are at high risk for developing hypertensive disorders during their adult lives. Although MND is uncommon in developed countries, it is still a major problem in many underdeveloped countries. In addition, MND is commonly used in animal models to mimic placental dysfunction, which leads to nutrient restriction to the fetus. One project, which is studying the effect of MND on the developing fetal kidney, found that MND results in permanent changes to the fetal kidney, leading to hypertension. Another NICHD-funded grant is studying pregnancy in a rat model to understand the mechanisms of abnormal kidney function. Although preliminary, data from this project are highly suggestive that maternal under-nutrition results may cause fundamental disruption in specific gene sequences, causing disruption in the formation of fetal nephrons. These preliminary studies provide insight into the mechanisms of kidney formation in infants with intrauterine growth restriction, forming a foundation for future preventive strategies.

NICHD works closely with NIDDK on issues related to kidney development and the consequences of abnormal development. NIDDK supports a robust portfolio of research into the development and function of the kidneys in children and adolescents, including studies of the hereditary causes of kidney disease and studies of cell fate and precursors of disease in kidney development. The Chronic Kidney Disease in Children study is defining novel risk factors for disease as well as early manifestations of disease in pediatric patients. The Randomized Intervention for Children with Vesicoureteral Reflux trial is comparing prophylactic antibiotic treatment with placebo for prevention of urinary tract infections and kidney scarring in children with reflux. NIDDK is currently conducting a “Kidney Research National Dialogue,” an effort to strategically plan its future research focus for kidney biology, development, and disease. The two Institutes recently cosponsored a funding opportunity announcement on congenital obstructive uropathy, one of the major causes of chronic kidney disease and end stage renal disease in infants and children. This funding opportunity solicits applications to address the numerous scientific and clinical uncertainties related to congenital obstructive uropathy by encouraging and facilitating research in diverse areas, such as the development of objective prognostic markers and reliable animal models for this disorder, genetic determinants, and evaluation of the long-term effectiveness of various treatment strategies.

Item

Orthotics and Prosthetics. - As America’s population ages, the demand for orthotic and prosthetic care to address the effects of stroke, diabetes, cardiovascular disease, and other health issues continues to grow. To date, little comparative effectiveness and outcomes research has been conducted to establish which patients benefit most from which orthotic and prosthetic services, supports, and devices. The Committee supports evidence-based research in prosthetic and orthotic care, and urges NICHD and the National Center for Medical Rehabilitation

Research to coordinate with DOD and the Department of Veterans' Affairs to develop and pursue a research agenda that responds to the most pressing needs of the field. (p. 88)

Action taken or to be taken

NICHD recognizes that gaps persist in comparative effectiveness and outcomes research concerning orthotic and prosthetic devices. One foundational challenge in this field, observed also by the NIH-appointed Blue Ribbon Panel on Medical Rehabilitation Research, is the current lack of adequate outcomes tools to measure the effectiveness of rehabilitation interventions. Although a relatively large number of instruments are designed to measure and evaluate mobility, for example, not all of them adequately factor in the patient's perspective or the clinician's ease of use. Accordingly, no single measure stands out as a universal solution, and none are appropriate for systematic implementation in assessing how orthotics and prosthetics affect an individual's ability to perform basic tasks of daily life. Collecting such information is an essential activity in the provision of evidence-based healthcare.

To improve outcome measures in orthotics and prosthetics, NICHD's National Center for Medical Rehabilitation Research (NCMRR) continues to support work at the University of Washington on a model outcome system for individuals with prosthetic lower limbs. The study's research team is working with the Department of Veterans Affairs at different sites across the country to recruit amputees to participate in the study. This work has the potential to facilitate future research, inform treatment strategies, and improve patient care. This project builds upon advances made in the trans-NIH Patient Reported Outcomes Measurement Information System (PROMIS) network, funded by the NIH Common Fund, previously the NIH Roadmap for Medical Research. Since 2004, the PROMIS initiative has been developing, testing, and implementing new approaches to measure patient-reported outcomes such as pain, fatigue, physical functioning, emotional distress, and social participation, which influence quality of life across a wide range of disorders. Other NCMRR-supported research projects in this area include comparison studies of prosthetic sockets and liners, and a large-scale prospective study of rehabilitation services and outcomes for veterans receiving amputations. These research efforts, if successful, have great potential for applicability to other rehabilitation populations, e.g. individuals with diabetes who have lost limbs due to amputation.

Meanwhile, NCMRR continues to be engaged actively with DOD and the Department of Veterans Affairs. NCMRR scientific program officers serve on review panels for the Department of Veterans Affairs Rehabilitation Research and Development Service; participate in planning and evaluation activities of the Telemedicine and Advanced Technology Research Center of the US Army Medical Research and Materiel Command; and, are in ongoing collaborations with the Defense Advanced Research Projects Agency, helping to develop concepts for advanced prosthetics. The Blue Ribbon Panel, whose report recently was submitted to the NIH leadership, recommended that NIH expand its coordination efforts with DOD, the Department of Veterans Affairs, and other federal partners. NIH actively is considering this and the Panel's other recommendations.

Item

Pediatric Functional Gastrointestinal Disorders [FGIDs]. - The Committee encourages NICHD to work with NIDDK to support research addressing FGIDs in children. (p. 88)

Action taken or to be taken

Functional gastrointestinal disorders (FGIDs) are characterized by chronic or recurrent abdominal symptoms without identifiable pathology. NICHD supports research designed to understand the biopsychosocial processes associated with pediatric chronic abdominal pain that place children at increased risk for FGIDs as adolescents and adults. One currently funded study will identify characteristics of youth with chronic abdominal pain who are most likely to experience psychiatric disorders as adolescents and young adults, suggesting factors that could be addressed in future prevention and treatment efforts. NICHD also supports a study that will evaluate a parent-only, social learning, and cognitive behavior therapy intervention, delivered in person for one group and by telephone for another group, aimed at reducing symptoms of functional abdominal pain in their children. If successful, this intervention could provide useful models for the development of effective, accessible interventions for FGIDs and other medical problems. In a randomized clinical trial supported by NICHD on unexplained abdominal pain, researchers found that parents and children that received cognitive-behavioral therapy reported less severe symptoms than a control group that received standard care, supporting the use of this intervention in children with abdominal pain.

NIDDK is supporting research on the collective genetic material of microbes (the “microbiome”) present in the intestines of children with FGIDs, such as irritable bowel syndrome (IBS) and constipation, compared to the microbes found in healthy children. By sequencing the genomes of microbes living in the intestines of these children, scientists have identified microbial “signatures” associated with pediatric IBS, and with subtypes of IBS with or without constipation. 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.

Item

Pheochromocytoma. - The Committee is concerned that the current funding for the diagnosis, pathophysiology, and molecular biology of pheochromocytoma is inadequate to meet the rapidly expanding patient base and growing need for research into pheochromocytoma and paraganglioma. The Committee recommends NIH expand the funds available for this effort. (p. 88)

Action taken or to be taken

Pheochromocytomas and paragangliomas are rare types of tumors. Pheochromocytomas form in the adrenal glands, while closely related paragangliomas originate in neuronal cells, which can be located throughout the neck, chest, abdomen, or pelvis. These tumors can produce abnormally high amounts of the hormones that control normal body stress reactions, heart rate, and blood pressure, among other functions. They can occur at any age, including in childhood,

although most commonly in middle age. NICHD and the National Cancer Institute (NCI) support and conduct research on pheochromocytomas and paragangliomas, largely through their intramural programs, to understand their causes, improve detection methods, and develop effective therapies. In addition, NIH welcomes competitive grant applications to study adrenal gland tumors and has supported scientific meetings to further knowledge in this area of research; NIH will continue to pursue research based on availability of funding.

Despite numerous biomarkers reported for various types of cancers, few are useful for predicting metastasis, a major cause of mortality in patients with cancer. A recent study, conducted by NICHD intramural scientists, uncovered a prohormone processing enzyme (carboxypeptidase E) that is elevated in benign pheochromocytomas at the time of surgery, providing a powerful prognostic marker for predicting future metastasis in different cancers. Other NICHD intramural researchers are exploring whether a patient's hereditary mutations can be determined through measurement of higher than normal metabolites in the blood; knowledge of specific disease-predisposing mutations can help health care providers personalize the required treatment and follow up. In the past year, NCI intramural investigators have characterized a new mouse model of neurofibromatosis-associated pheochromocytoma. They have used the model to identify an area on mouse chromosome 16 that influences susceptibility to pheochromocytoma. This area affects only females, suggesting that there may be differences in pheochromocytomas between men and women. In collaboration with investigators at NICHD, NCI intramural investigators have compared patient pheochromocytomas to those in the mouse model to identify candidate genes in the area. If confirmed in patients, modifier gene(s) in this area may help to predict who is at risk for pheochromocytoma and suggest new treatments.

NIH supports a variety of clinical trials related to pheochromocytomas and paragangliomas. In one NICHD-supported study, researchers examined the age of patients when they are diagnosed and the hormones that are released by their tumors, and found that patients with epinephrine-producing tumors were diagnosed 11 years later than patients with tumors that did not produce epinephrine, a neurohormone. Two current NCI intramural clinical trials include: a trial to examine the effectiveness of an investigational drug called ZD6474 (vandetanib) to prevent the growth and development of new blood vessels on tumors associated with von Hippel Lindau disease (a rare genetic disease), including pheochromocytomas, , and a genetic study to characterize the natural and clinical histories of patients with inherited urologic malignancies, including pheochromocytomas. Intramural researchers reported that, based on surgeries performed at NCI from 2007 to 2010, robot-assisted laparoscopic partial adrenalectomy for pheochromocytoma is a safe and feasible technique and provides encouraging functional and oncologic outcomes.

Item

Preeclampsia. - The Committee is concerned by the lack of progress made in understanding the causes of and risks associated with preeclampsia and the related conditions of eclampsia and HELLP syndrome, which can result in disability or death for a mother and premature delivery or death for an infant. The Committee encourages NICHD to work with other ICs to share research findings and facilitate additional research into ways to better prevent, manage, and identify interventions for these conditions. (p. 88)

Action taken or to be taken

NICHD works in collaboration with other NIH Institutes and agencies to understand the causes of and risk associated with pregnancy-associated hypertension including preeclampsia, eclampsia and related conditions. Although to date these efforts have not identified interventions or predictors, progress has been made.

Steady progress is being made in the basic understanding of preeclampsia. Earlier research focused on oxidative stress, but clinical trials showed that this was not the causal factor. Currently, scientists believe that preeclampsia is associated with a uterine defect that leads to inadequate blood supply to the placenta, which in turn, can result in damage to the maternal endothelium and other organ damage. Additional studies investigate the contribution of the immune system to the disease; one investigator has found that a maternal antibody can be present in preeclampsia. He has successfully induced preeclampsia in animal models by adding this antibody, and then reversed the effect with a neutralizing autoantibody peptide. The use of the neutralizing autoantibody peptide to treat preeclampsia may be a promising therapy if found safe and effective in future human trials.

In 2010, NICHD established the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b), an ongoing study of women for whom the current pregnancy will lead to their first delivery. This group of women comprises about 40 percent of pregnant women in the United States and is the group at highest risk for developing preeclampsia. NuMoM2b is a prospective cohort study of 10,000 racially, ethnically, and geographically diverse women who will undergo thorough research assessments during the course of their pregnancies to help understand the mechanism and predictive factors related to preeclampsia and other adverse pregnancy outcomes. By determining the maternal characteristics, including genetics, clinical, environmental, and physiological factors that influence and/or predict the development of preeclampsia in the first pregnancy, nuMoM2b will be able to determine the women at highest risk for development of preeclampsia, and allow targeted interventions to be developed.

Further, several recent studies have demonstrated that statins might fill the current gap to prevent the recurrence of preeclampsia. NICHD is evaluating the effect of early treatment with pravastatin in the prevention of an imbalance of proteins related to the formation of blood vessels in the placenta that are associated with preeclampsia. If successful, the pharmacologic data generated from this study will form the basis for future clinical trials for this potential treatment.

Estimates show that preeclampsia may affect up to 10 percent of pregnancies in the developing world. NICHD's Global Network for Women's and Children's Health Research has completed a randomized controlled trial of emergency obstetric and neonatal care to reduce maternal and neonatal deaths in seven research sites in India, Pakistan, Guatemala, Kenya, Zambia, and Argentina. A package of interventions were implemented to improve prenatal care, including identifying women with signs of preeclampsia, stabilizing affected women, and arranging for transport to facilities where cesarean sections could be safely performed, thus improving the outcomes for both mother and baby.

Item

Preterm Births. - The Committee commends NICHD on its work to prevent preterm births and encourages the Institute to take into account that there are a number of conditions which increase the risk of neurologic damage. The Committee urges NICHD and NINDS to undertake studies into interventions during pregnancy and/or labor to improve neonatal outcome, particularly neurologic outcome. The Committee also requests that NICHD identify the steps necessary to establish one or more transdisciplinary research centers for prematurity as recommended by the IOM. (p. 88)

Action taken or to be taken

NICHD, along with other NIH Institutes and Centers, is strongly committed to reducing preterm birth, to understanding its causes, and to identifying interventions for both mothers and premature babies that will optimize their neurologic and other health outcomes. The Institute carries out these efforts through an extensive portfolio of investigator-initiated research and targeted clinical studies conducted by transdisciplinary networks of researchers, as recommended by the IOM. For example, the goal of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) is to elucidate how combinations of genes, proteins and/or biomarkers along with demographic and environmental factors may predict preterm birth. The Genomics and Proteomics Network brought together experts in genomics and proteomics with clinicians, statisticians, and epidemiologists, to apply advances related to other conditions (such as cardiovascular disease) to the field. This group examined the potential genetic and environmental causes and mechanisms of spontaneous preterm birth, with the objective of identifying biomarkers of increased preterm delivery risk, with the ultimate goal of designing effective prevention strategies.

NIH-supported research also focuses on improving neurologic neonatal outcomes. NICHD's Maternal and Fetal Medicine Units network is conducting a trial comparing types of fetal heart rate monitoring and NICHD's Neonatal Research network has ongoing trials to refine how to optimize brain cooling strategies for compromised infants to improve neurologic outcome. Another trial investigated continuous positive airway pressure compared to intubation with surfactant administration after delivery room stabilization in infants born at 24-27 weeks gestational age. Examples of current NINDS-supported research include a long-standing neonatal brain disorders research center based at the University of California, San Francisco, with additional collaborating institutions in the United States and abroad. The center conducts basic and clinical research on the mechanisms of injury and recovery following incidences of oxygen deficiency in the brains of full term and premature infants. Another collaborative research project focuses on growth factor and other cellular signaling pathways involved in recovery from hypoxia that may lead to therapy development.

In addition, NICHD's intramural Perinatology Research Branch, which conducts clinical and laboratory research on maternal and fetal diseases responsible for infant mortality, has contributed substantially to our basic understanding of preterm birth, with a particular focus on the role of uterine infections and inflammation. The branch recently completed a multinational study that showed that the administration of vaginal progesterone (a natural hormone involved in pregnancy maintenance) to women with a short cervix reduced the rate of preterm birth by 45

percent, and reduced the rate of respiratory distress syndrome by 61 percent. Follow-up studies are currently being conducted in the United States and Europe.

Preterm births account for approximately one-third of all neonatal deaths in the developing world. Although the evidence that a course of antenatal glucocorticoids improve preterm survival by maturing the brain, lungs, gut, and skin is very strong in developed countries, it is not clear that antenatal glucocorticoids will be effective in the developing world where specialized care is generally not available. NICHD's Global Network for Women's and Children's Health Research is enrolling 40,000 women in a randomized controlled trial of antenatal glucocorticoids to improve the outcome of 4,000 preterm infants in six developing countries in collaboration with the World Health Organization. The Global Network also is collaborating with the World Health Organization, the Gates Foundation, and March of Dimes on *Born Too Soon* which seeks to ensure that all women at risk of preterm delivery in the developing world have access to antenatal glucocorticoid treatment.

Item

Severe Maternal Morbidity. - The Committee understands that NICHD is exploring the feasibility of holding a scientific workshop to harmonize definitions for maternal morbidity. The Committee urges NICHD to reach a positive decision, as uniform definitions would help Federal, State, and local agencies and research institutions establish standardized and interoperable processes for surveillance, data collection, and research. (p. 88)

Action taken or to be taken

The definition of "severe maternal morbidity" and related morbidities is complex and varied across surveillance, data collection, and research efforts. Examples of these morbidities include hemorrhage, infection, hypertensive disorders of pregnancy (preeclampsia, eclampsia, and related conditions), and obstructed labor. Although the United States does not routinely monitor maternal morbidities, several countries do (see, for example, the Scottish Confidential Audit of Severe Maternal Morbidity 8th Annual Report 2010, http://www.healthcareimprovementscotland.org/programmes/reproductive_maternal_child/programme_resources/scasmm.aspx).

In preparing to develop a scientific workshop in this area, NICHD was invited to participate in a national meeting by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance aimed at revitalizing the data definitions for obstetrics and perinatal care (ReVITALize). These organizations and others have been working to develop nationally standardized definitions. The goal of this national collaborative, is to harmonize definitions and data elements across all organizations, across federal and state governmental entities, and across vital statistics collection efforts, electronic health records, clinical and patient registries, and research databases, to ensure that data sharing and aggregation can provide the qualitative information needed to provide the best care for women and newborns now and in the future. Rather than duplicate these efforts, NICHD has participated and encouraged grantees to participate in this seminal project. NICHD anticipates that this effort, with input from so many stakeholders, will provide comprehensive definitions including those for severe maternal morbidity.

In addition, NICHD has identified specific terms within the context of maternal health that may require additional discussion, such as determining the definition of a “term” birth. The national emphasis on reducing preterm birth has raised questions about whether the definition of births that reach “term” should be changed to exclude deliveries in the 37 or 38 weeks of pregnancy, since growing evidence indicates that healthy pregnancies should be delivered after 39 weeks if possible. NICHD will hold a scientific workshop in December 2012 to review the evidence, evaluate the implications of changing the definition of “term” births, and discuss dissemination of the workshop’s conclusions to professional societies and health organizations.

Standardization of these definitions in the U.S. would allow surveillance, data collection, and research efforts to be harmonized with parallel international activities, particularly critical to maternal health since the great majority of pregnancy-related maternal morbidity and mortality occur in developing countries.

Item

Spinal Muscular Atrophy [SMA] Care Protocols. - The Committee is aware that clinical practice guidelines for SMA are under preliminary development by advocacy groups in concert with expert investigators and clinicians. In the absence of evidence-based care protocols, the efficacy of the care received by SMA patients depends largely upon geographic proximity to experienced care centers and clinicians. Many SMA patients receive care that is inconsistent with best practices, and this variability negatively impacts individual patients as well as clinical trial results for SMA therapies. The Committee encourages NICHD to support natural history and care studies of SMA to facilitate the development of clinical practice guidelines that will bring uniformity to the medical care received by SMA patients and significantly improve the management of the disease. The Committee further encourages NICHD to facilitate the sharing of data and data sources between stakeholders involved in such studies. (p. 88-89)

Action taken or to be taken

Spinal muscular atrophy (SMA) is one of the most common lethal genetic diseases. Over the past decade, the development and increasingly widespread implementation of standard of care protocols and proactive nutritional as well as respiratory support has dramatically improved survival in babies with SMA type I, a severe variety of the disorder which accounts for more than 50 percent of affected children. However, NIH is working to gain a better understanding of when and how to best treat each of the different types of SMA, which will call for children to be identified early and followed to gain an understanding of the course of the different types of SMA as well as the efficacy of different types of treatments. While NIH does not develop clinical practice guidelines, it does support research to inform the development of practice guidelines by professional medical societies in association with patient organizations.

To add to the body of evidence on SMA, in 2011 NICHD funded a pilot newborn screening project for identification and follow-up of infants with SMA. The five-year study is exploring the ethical, regulatory, and policy issues regarding the use of state newborn screening programs to screen for SMA. The project is developing a model consent protocol and informational materials for parents and key stakeholders, and is implementing a multi-state newborn screening

pilot to assess the feasibility of a DNA-based test to identify infants at risk for SMA. The children identified through newborn screening also will be followed across time to gain an understanding of the progression of the disease from birth onward.

Based on an earlier conference sponsored by NINDS, a group of SMA researchers and clinicians formed the Spinal Muscular Atrophy Standard of Care Committee which, following an extensive planning process, published the “Consensus Statement for Standard of Care in Spinal Muscular Atrophy” in 2007 (*J Child Neurol* 2007 22: 1027; <http://jcn.sagepub.com/content/22/8/1027>). NINDS also is supporting a Common Data Elements (CDEs) Project to develop data standards for clinical research and harmonize data collection across clinical studies on neurological disease. Central to this project is the creation of common definitions and data sets so that information (data) is consistently captured and recorded across clinical trials. While developing CDEs for neuromuscular diseases, NINDS recognized the need to develop SMA specific CDEs for the research community. Thus, an SMA CDE Working Group, including NICHD, was formed in February 2012 and was charged with reviewing the neuromuscular CDEs to determine additional elements that would be useful for an SMA-specific study. The SMA CDEs contain recommendations within the following areas: External Devices; Family History; Medical History; Motor Milestones and Current Level of Function; Surgical and Hospitalization History; and Pediatric and Adult Clinical Outcomes. The neuromuscular disease and SMA CDEs are now available at <http://www.commondataelements.ninds.nih.gov/NMD.aspx>. These recommendations were made available to the Muscular Dystrophy Association for incorporation into a comprehensive clinical registry for neuromuscular diseases.

Another NINDS effort, the recently established Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), is working to help ensure consistency across clinical trials in neurological disease, including those focused on neuromuscular disease and SMA, specifically. As a multi-disease network, NeuroNEXT will reduce delays in building infrastructure for each new trial and streamline the clinical trial process. The first clinical research funded by NeuroNEXT is an SMA biomarkers study. Biomarkers are objective measures of the disease process or the biological actions of candidate therapeutics, and may aid in critical SMA therapeutic clinical trials in the future.

Item

Vulvodynia. - The Committee is pleased with the progress that NICHD has made over the last fiscal year in expanding extramural research support for vulvodynia, ensuring adequate representation of vulvodynia experts on peer-review panels, convening a vulvodynia workshop, and developing a research plan on this condition. The Committee calls upon the Director to build upon these initial efforts by carrying out the recommendations from the strategic research plan and expects to be updated on the Institute’s progress in the fiscal year 2014 congressional budget justification. The Committee also notes that vulvodynia frequently coexists with other persistent pain conditions, including interstitial cystitis, fibromyalgia, temporomandibular disorders, irritable bowel syndrome, endometriosis, headache, and chronic fatigue syndrome. The Committee is pleased with NICHD’s participation in the trans-NIH research initiative to support studies aimed at identifying etiological and mechanistic pathways of these overlapping conditions, and the Institute is encouraged to continue its work in this area. (p. 89)

Action taken or to be taken

Recognizing the lack of basic information about the chronic pain condition of vulvodynia, NICHD sponsored a scientific meeting in late FY 2011, bringing together a diverse group of scientists, clinicians, and patients to examine existing evidence and delineate the similarities and differences of vulvodynia from other chronic pain conditions. In formulating recommendations for research areas, participants agreed that without a fundamental understanding of vulvodynia – its mechanisms, its causes, and even its prevalence – developing effective treatments would be difficult. In response, NICHD, in collaboration with the Office of Research on Women’s Health (ORWH) and other NIH Institutes and Centers, released the *NIH Research Plan on Vulvodynia* in April 2012 (http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5781) that outlines research goals aimed at moving the field toward identifying new treatments for this spectrum of conditions.

The research plan identifies many areas of scientific opportunity within the relatively new field of vulvodynia research, such as basic physiological research on vulvodynia specifically and in the context of other pain disorders. Treatment-related research was identified as a high priority. Objectives include determining whether compounds that have been effective in blocking central, peripheral, and mixed pain are suitable for testing in vulvodynia patients. Underpinning all of these efforts, however, is the need to develop reliable, valid, and standardized measures for diagnosis and outcome measurement to further epidemiological and casual studies. Consistency in evidence-based definitions would allow for comparisons across studies and enable the field to advance more quickly. To that end, NICHD is planning to host a follow-up scientific meeting in May 2013, to forge consensus on some of these definitional issues, specifically the development of research and/or clinical criteria for vulvodynia. Planning for this essential meeting is under way.

In the meantime, NICHD has increased its investment in research related to vulvodynia. In 2012, several new grants were funded in response to a funding opportunity announcement co-sponsored by NICHD and ORWH. The purpose of the announcement was to solicit applications that address basic, clinical, translational, epidemiological, or behavioral research on vulvodynia. Results from a study funded by NICHD through this announcement found that women with vulvodynia are two to three times more likely than other women to suffer from other chronic pain conditions, such as interstitial cystitis, inflammatory bowel syndrome, or fibromyalgia.

NICHD also participates in trans-NIH efforts to address pain conditions, such as the NIH Pain Consortium, and the workshop sponsored by several Institutes and Centers that was held in 2012 on vulvodynia and other overlapping chronic pain conditions. Sponsored by the NIH Overlapping Chronic Pain Conditions Working Group, the workshop focused on the current understanding of chronic overlapping pain conditions, their etiology, risk factors, mechanisms of disease, outcome measures, and diagnosis. The goal of the workshop was to develop a coordinated research strategy that addresses underlying etiology, the trajectory of disease, risk factors, and approaches for developing outcome measures and diagnosis of these conditions. A report on the meeting’s findings is currently under development.

National Eye Institute (NEI)

Senate Significant Items

Item

Diabetic Eye Disease. - The Committee continues to support the important work of the NEI Diabetic Retinopathy Clinical Research Network. (p. 89)

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 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 implement protocols and recruit patients rapidly for large-scale clinical trials. The development of Lucentis, the first FDA approved drug for age-related macular degeneration (AMD), allowed DRCR.net to evaluate its use in diabetic macular edema (DME), which like AMD, leads to visual impairment when damaged or abnormal blood vessels leak fluid into the retina. Lucentis, with standard-of-care laser treatment, significantly improved vision in nearly 50 percent of patients. In August 2012, the FDA approved Lucentis for DME, making it the first new therapy for DME in 20 years. This landmark finding spurred DRCR.net to launch a new clinical trial in early 2012 evaluating Lucentis in proliferative diabetic retinopathy (PDR), a more advanced form of diabetic eye disease where fragile blood vessels grow into the retina.

In addition to Lucentis, two other drugs, Avastin and Eylea, have become used widely for AMD. In August 2012, the DRCR.net launched a clinical trial to compare the three drugs in the treatment of DME. This trial will examine the safety and efficacy of commonly used therapies for DME, allowing patients and doctors to make more informed treatment choices.

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 identifying more than 500 genes associated with both common and rare eye diseases, enabling an understanding of disease mechanisms and development of potential therapies for such blinding eye conditions as age-related macular degeneration [AMD], glaucoma, and retinitis pigmentosa [RP]. The Committee is pleased that NEI's AMDGene Consortium has validated eight previously known gene variants and identified 19 new gene variants, and that the NEI Glaucoma Human Genetics Collaboration [NEIGHBOR] has identified the first risk variant in a gene thought to play a role in the

development of the optic nerve head, the degeneration of which leads to glaucoma and loss of peripheral vision. (p. 89)

Action taken or to be taken

Over the past several years, great strides have been made in our understanding of age-related macular degeneration (AMD). Researchers identified susceptibility genes which have implicated the immune system, cholesterol, and extracellular protein pathways in the disease. Understanding how gene variants in these pathways lead to disease is the next step in the process of developing rational therapies that address the root cause of AMD. While this work progresses, NEI continues the search for other gene variants that may lead to disease. Many of these genes are likely rare variants that affect less than 5 percent of patients and are undetectable through genome wide association studies. Thus, the AMD Gene Consortium is employing new, cost-effective genotyping technologies developed to evaluate the contribution of rare gene variants in disease susceptibility. Using customized gene screening technology, the Consortium will examine approximately 14,000 advanced AMD cases, 6,000 cases of less advanced disease, and 18,000 geographically matched controls. With this effort, the Consortium expects to identify most, if not all, of the remaining genes implicated in AMD.

Genome-wide association studies, including the NEI Glaucoma Human Genetics Collaboration (NEIGHBOR) study, have identified five genes/loci that are statistically associated with primary open angle glaucoma (POAG), the most common form of glaucoma. While these results are encouraging, they also suggest that large datasets with rich clinical data are needed to delineate the genetic nature of glaucoma. To this end, NEI is creating NEIGHBORHOOD (**NEIGHBOR Heritable Overall Operational Database**) consortium and database. The goals of NEIGHBORHOOD are to expand the collection of glaucoma cases and collect exacting clinical data to classify the subtle variations of the disease. NEIGHBORHOOD will include cases and controls from the Nurses' Health Study and Health Professionals Follow-up Study, the Women's Genome Health Study, Mayo Clinic, Marshfield Clinic, and the University of Iowa Ophthalmology clinics. NEIGHBORHOOD will create a rich resource for future studies of other POAG related traits as well as gene-gene and gene-environment interactions.

Item

Translational Research. - The Committee recognizes NEI's translational research initiatives and is pleased that the NEI-led human gene therapy clinical trial for Leber congenital amaurosis has resulted to date in 15 patients being treated and experiencing visual improvement. The Committee applauds NEI's pioneering work that is enabling further research into ocular gene therapy through the launch of clinical trials for AMD, choroideremia, Stargardt disease, and Usher syndrome, as well as pre-clinical safety trials for RP, juvenile retinoschisis, and achromatopsia. (p. 89-90)

Action taken or to be taken

Clinical trial work in Leber congenital amaurosis (LCA) is currently focused on increasing the treatment dosage with additional injections and treating the better eye. Results of these studies are expected in 2013. In the meantime, efforts to advance new gene therapy treatments continue in a dramatic fashion.

In 2012, a team of NEI-funded scientists used gene therapy to reverse an aggressive form of X-linked retinitis pigmentosa (XLRP) in canines caused by a mutant copy of the *RPGR* gene. This finding holds enormous potential as it suggests treatment is still possible after disease onset. In all forms of retinitis pigmentosa, the disease damages light sensing cells in the retina called photoreceptors and causes gradual vision loss that leads to blindness. This study, which parallels the early efforts to develop gene therapy for LCA, provides strong evidence this approach might also work in humans.

Work to advance XLRP gene therapy is now focused on identifying the critical period during the course of the disease when treatment will be most effective. Determining how late in the course of the disease a therapeutic effect can still be achieved will be essential when selecting patients for potential clinical trials. Efforts are also under way to approximate the normal level of *RPGR* gene activity to avoid any potential adverse events that might be associated with over expression of the gene. Lastly, scientists must ensure that the treatment is durable and safe. Hopefully, these efforts will culminate in an effective treatment for a severe form of RP that leaves most patients legally blind before age 45.

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National Institute of Environmental Health Sciences (NIEHS)

Senate Significant Items

Item

Endocrine Disruption and Women's Health. - The Committee urges NIEHS to increase its research on the effects of endocrine disrupting chemicals on women's health outcomes. An update is requested in the fiscal year 2014 congressional budget justification. (p. 90)

Action taken or to be taken

NIEHS supports a wide variety of studies on the effects of endocrine disrupting chemicals (EDCs) and is committed to expanding its research investment in this area. EDCs are a group of structurally diverse compounds that include pharmaceuticals, dietary supplements, industrial chemicals, and environmental contaminants that can elicit a number of adverse health effects in women, including hormone dependent cancers, reproductive abnormalities, compromised reproductive fitness, and impaired cognition. NIEHS currently funds over 200 grants (more than 25 percent of total NIEHS grants) focusing on EDCs, including grants focusing on exposure to EDCs during pregnancy, as well as on men's and women's reproductive health. This portfolio is divided approximately equally between human epidemiology studies and animal mechanistic studies.

In January 2012, NIEHS and the Collaborative on Health and the Environment, a non-partisan partnership of research, professional, and disease advocacy groups, organized a new women's reproductive health consortium. The group's goal is to foster interactions, data sharing, and collaborations to increase research on women's reproductive health and its impact on public health policy. The consortium, which includes more than 40 NIEHS grantees, meets monthly and plans to hold a workshop in January 2013. The consortium is currently working to develop a review of the effects of increased estrogenic EDCs on women's reproductive health, as well as expanding research into diethylstilbestrol in humans and animals exposed during pregnancy.

NIEHS also provided funding support and expertise in 2012 for a World Health Organization update on the state of the science in endocrine disruptors. Because the majority of EDCs are estrogenic, this review includes a major focus on women's health issues. Also in 2012, NIEHS announced an initiative to understand the role of EDC exposures throughout life, but especially during development, on the risk of obesity and Type 2 diabetes. These diseases are increasing in the general population, but are more prevalent in women and affect women's overall health, including their reproductive health.

NIEHS grantees, using an animal model, have shown that the risk of uterine fibroids is increased with exposure to specific estrogenic EDCs when the exposure is during pregnancy. This research also showed that the fibroids occur later in life, long after the exposure. Other recent studies highlight the potential of girls with higher body weight to accumulate endocrine disruptors commonly found in plastics, and that these exposures contribute to further weight gain, changes in progression through puberty, and breast cancer risk. Significant headway is being made in identifying biomarkers in the blood and urine that could lead to early screens for

metabolic disorders that can lead, later in life, to breast cancer and related diseases.

Item

Gulf Oil Spill. - The Committee commends NIEHS for the Gulf Long-Term Follow-Up [GuLF] Study of 55,000 clean-up and response workers whose activities have involved potential exposures to oil, combustion by-products from burning oil, and oil dispersants that may be associated with adverse health consequences. In addition, the Committee commends the National Toxicology Program for its assessment of the toxicological effects of crude and weathered oil and dispersants, as well as NIH for its grants to community-university consortia for research on the effects of the oil spill on the health of the people of the gulf coast. The Committee urges NIEHS and other Institutes to continue their support of these important studies. (p. 90)

Action taken or to be taken

NIEHS continues to pursue research on the impacts of the Gulf Oil Spill. Updates on the various research activities are listed below.

- **Gulf Long-Term Follow-Up (GuLF) Study:** The GuLF STUDY is the largest ever study of the potential health effects associated with an oil spill. The study is focused on both physical and mental health effects related to the oil spill and is collecting information that can be used by individuals, communities, and governments to better understand the consequences of oil spills and plan for the future. The study began enrolling clean-up workers and others who helped with the oil spill clean-up in any way in February 2011. Participants complete a telephone interview, in English or Spanish, which collects detailed information on experiences during the oil spill clean-up and current health. The response to the study has been excellent, with more than 100 community and professional groups supporting the effort. As of February 26, 2013, about 33,000 people have joined the study and the study started to wind down their enrollment activities. About 10,500 persons from Gulf state communities have completed a home visit that includes a brief clinical assessment and collection of blood and other biospecimens. As many as 11,500 home visits will be completed by June 2013.
- **Extramural Consortia:** NIEHS is leading a trans-NIH effort involving NCI, NHLBI, NIMH, NIMHD, NINR, NCATS, and OBSSR that has awarded a total of \$25.1M (\$21.9M from NIH appropriations and \$3.2M from the BP Gift Fund) over five years in research grants to Gulf area universities that partner with communities affected by the oil spill. The four grant recipients (Louisiana State University, Tulane University, University of Florida and University of Texas Medical Branch at Galveston), in partnership with impacted communities, will examine the potential harmful effects of the Deepwater Horizon disaster on reproduction and birth outcomes, the cardiorespiratory system, and behavior and mental health of children and adults in the general population. These programs have already begun to recruit participants for various studies, conduct interviews, and collect data. The interplay of these multiple stressors on human health will be important in establishing the evidence base for recovery efforts, and developing strategies to improve health in this and future disasters.

- **National Toxicology Program (NTP):** Currently the NTP is pursuing several lines of research to address concerns regarding the safety of Gulf seafood, hazards to offshore and onshore cleanup workers, and potential long-term health impacts of residual oil in the environment. Analytical chemistry studies are being conducted to better understand the composition of the source oil and tar balls and oiled sediment collected along the shoreline. The focus of these analyses is on components that are more likely to persist in the environment and potentially lead to residual human exposures. The NTP is using this analytical information to develop a toxicology research program on polycyclic aromatic hydrocarbons (PAHs). The aim of this program is to further characterize the hazard of PAHs present in oil and to better understand how differing combinations of individual PAHs may affect toxicity and safe exposure levels.

In addition to these efforts, NIEHS programs are now partnering with the Substance Abuse and Mental Health Services Administration to enhance research efforts to examine the behavioral and mental health issues related to the oil spill.

Item

Women’s Health and the Environment. - The Committee urges NIEHS to increase its research in several areas of special importance to women’s health: exposures that may initiate or promote autoimmune diseases; exposures associated with risk of uterine fibroids; the effects of engineered nanomaterials in consumer products, especially cosmetics and personal care products; and environmental exposures that are associated with increased time to pregnancy. (p. 90)

Action taken or to be taken

NIEHS approaches women’s health research through defining underlying susceptibilities to female-predominant diseases, investigating the role of environmental agents, identifying environmental triggers for their development and factors that can reduce risk, and determining the importance of timing of exposure to disease risk.

A September 2010 NIEHS Expert Panel Workshop brought together researchers to evaluate the state of the science regarding the role of the environment in the development of autoimmunity and related diseases. Among the consensus findings were that exposure to crystalline silica, certain solvents, and smoking can contribute to the development of various types of autoimmune diseases. In addition, the Panel found an inverse association between ultraviolet radiation exposure and development of multiple sclerosis. Much remains to be known in understanding autoimmune diseases, but further investigation will improve diagnosis, treatment, and possibly allow for future preventative strategies.

The NIEHS-funded Sister Study is investigating a wide range of ways the environment may influence disease in women, including the development of uterine fibroids. Findings suggest that early-life exposures to diethylstilbestrol (DES), gestational diabetes, and having been fed soy formula may play a role in fibroid development. Other NIEHS-funded scientists have found that

exposure to endocrine disrupting chemicals during early infancy can increase the risk of developing fibroids.

The NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR) consortium was formed in November 2010 to gain fundamental knowledge on the health effects of engineered nanomaterials (ENMs). A part of these efforts is focused on understanding the influence of ENMs on women's health. These studies are exploring how ENMs may affect various physiological conditions such as pregnancy, lactation, and the health of the fetus. These investigations also include developing mathematical models for the disposition and effects of nanoparticles in order to provide a firm basis for predicting exposure conditions in women under which such materials could elicit adverse effects in the mother, fetus, or neonate.

NIEHS researchers are studying how environmental exposures may adversely affect pregnant women. For example, in one of the largest studies conducted to date, NIEHS funded researchers report that exposure to flame retardant compounds (polybrominated diphenyl ethers or PBDEs) is associated with decreased levels of thyroid stimulating hormone around the beginning of the third trimester of pregnancy. The research team measured PBDE and thyroid hormone levels in pregnant women, most of whom were Mexican American. Lab analyses showed that women with higher levels of PBDEs had lower levels of thyroid stimulating hormone, which plays an important role in fetal development. Future studies planned by the team will examine whether maternal exposure to PBDEs is associated with adverse pregnancy outcomes such as preeclampsia, premature birth, and low birth weight.

PBDEs have increased exponentially over the last three decades and serum concentrations of PBDEs are about 20 times higher in the United States than in Europe. This is of concern not only for pregnant women, but also for women who wish to become pregnant. NIEHS studies link higher exposure levels of PDBEs with increased time to pregnancy.

The NIH Office of Research on Women's Health, in collaboration with NCI, supported a study to identify environmental and genetic risk factors for inherited endometrial cancer. Additionally, the NIH Strategic Plan for Women's Health and Sex Differences Research includes recommendations from topical scientific working groups including one on women's health and the environment. This working group prioritized the need to understand the effects of chemical and other exposures on disease etiology in women, including a major focus on developmental programming of adult diseases and syndromes;
http://orwh.od.nih.gov/research/strategicplan/ORWH_StrategicPlan2020_Vol2.pdf.

National Institute of Environmental Health Sciences (NIEHS) Superfund

House Significant Items

Item

Worker Training Program. - The Committee recommends \$74,928,000 for the National Institute of Environmental Health Sciences, \$4,000,000 below both the fiscal year 2012 enacted level and the budget request. The Committee remains highly supportive of NIEHS' worker training program and notes the program trained 143,000 workers last year, teaching those participants how to reduce the risks of exposure to hazardous materials. This program has been offered to workers for years at no charge wherein many other governmental training programs include a course fee. The Committee directs NIEHS to explore the feasibility of incorporating a nominal fee to recoup administrative or other costs associated with the worker training program. NIEHS should include a report that summarizes findings and recommendations with the fiscal year 2014 budget request. (p. 83)

Action taken or to be taken

The NIEHS Worker Training Program (WTP) is a long-standing initiative that provides job training to a population that includes underserved, low-income, and/or jobless individuals through a diverse set of grantee institutions, and does so very efficiently with low overhead. NIEHS has taken a careful look at the program mission and objectives and has reviewed data from the grantees related to how they provide their services as well as any program income generated from training programs that they provide. Given the program objectives, and in light of the characteristics of both the variety of grantee institutions and the trainee population served, NIEHS finds that it would be both administratively difficult and counterproductive to the mission of the program to attempt to impose a fee across the board for trainees to have access to the program offerings.

The WTP is an umbrella consortium which is responsive to several statutory mandates (section 311(a) of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended, and section 126(g) of the Superfund Amendments and Reauthorization Act of 1986; USC42-9660, Section 9660(a).) The WTP consortium builds upon Federal-level partnerships that have been created over the last 20 years. The family of WTP programs includes the Hazardous Waste Worker (HWW) training program, the Minority HWW training program, and the Department of Energy (DOE) Worker training program, which is funded by DOE. Grantee organizations come from many different places, including academic consortia developed at four-year universities; Historically Black Colleges and Universities; Community Colleges; industry based colleges; non-profit organizations dealing with occupational health; labor based unions; and other groups. Each of these groups of institutions uses different business models to run their programs and deliver training in a cost-effective way for their target populations. Charging training fees has always been an option, but not a program requirement. Over the life of the program, very few of these organizations have charged for the training courses they provide. Our analysis found that only 3 out of 20 grantees generated program-related income during FY 2010 for the HWW training program, and no grantees did so for the Minority Worker or DOE programs.

The feasibility of incorporating a fee structure into the terms and conditions of the current cooperative agreements presents a number of administrative, legal, and financial challenges, depending on the specific business model employed by each grantee. A variety of approaches are incorporated into the training process to ensure an equitable public-private partnership in expending appropriated funds. For example, the Steelworkers Union generates program-related income by soliciting funds from employers to enhance the training that is provided. Some university groups also charge nominal fees depending on the target audience for the training. Some targeted groups, such as unemployed or disadvantaged groups, are not able to pay for training; thus, no charges are levied.

National Institutes of Health (NIH) policy, as stated in the NIH Grants Policy Statement (last revised, 2012), allows for program-generated income to be proposed by the applicant organization. Program income is defined as gross income—earned by a grantee, a consortium participant, or a contractor under a grant—that was directly generated by the grant-supported activity or earned as a result of the award. Program income includes, but is not limited to, income from fees for services performed; charges for the use or rental of real property, equipment or supplies acquired under the grant; the sale of commodities or items fabricated under an award; charges for research resources; registration fees for grant-supported conferences; and license fees and royalties on patents and copyrights. The grantees are permitted to utilize program income using the additive alternative, in which program generated income is added to funds committed to the project or program and used to further eligible project or program objectives. For the WTP, in the few cases where program income has been generated, the limited funds generated have been used to buy supplies and equipment for trainings or for instructor and curricula development. The amount of program income earned and expended must be reported on the appropriate annual financial report.

NIEHS is further reviewing existing Grants Management Policy for the Department of Health and Human Services (HHS) and NIH, to inform any changes in our approach towards program income. This includes analysis of administrative costs associated with collecting, distributing, and using optimal processes for retaining fees from trainees, employers, or the organizations that provide the training through the retention of program income or other methods for revenue capture. A variety of challenges would be expected with the incorporation of a fee for recouping costs, which may limit the viability of this option for some, if not all, grantees.

NIEHS considers that, given the wide variety of grantee institutions serving the WTP, the low income of most of the target populations, and the existing very low overhead cap of the program, it would not be feasible to mandate a fee collection model across the board. However, that does not mean that individual grantee programs could not choose to take advantage of existing policy to enhance their offerings. As NIEHS develops the next Funding Opportunity Announcement (FOA) for soliciting and competing for new cooperative agreements for this program in FY 2015, we will clarify the option under current policy for grantees to generate program-related income where appropriate.

National Institute on Aging (NIA)

Senate Significant Items

Item

Alzheimer's Disease. - In order to build upon the strong body of work already being done in NIH-funded Alzheimer's Disease Research Centers, the Committee urges NIH to take advantage of existing well-characterized, longitudinal, population-based cohort studies and the existing research infrastructure these large-scale cohort studies have already established to provide new insights into risk factors and protective factors related to cognitive decline and dementia. The Committee feels strongly that additional research is needed in minority populations that are at particularly high risk for cognitive decline and dementia. (p. 90)

Action taken or to be taken

NIA supports a number of large-scale cohort studies, and such studies are an invaluable resource for identifying risk and protective factors related to cognitive decline and dementia. For example:

- In FY 2012, NIH allocated an additional \$50M to Alzheimer's disease (AD) research under the President's Alzheimer's Initiative. A portion of these funds was dedicated to analysis of whole exome and genome sequencing data from thousands of participants through a collaboration between AD geneticists and the National Human Genome Research Institute Large-Scale Sequencing Program. Program goals are to identify new risk and protective genes, provide insight as to why individuals with known risk factor genes escape from developing AD, and identify potential avenues for treatment and prevention.
- The Baltimore Longitudinal Study of Aging (BLSA), America's preeminent study of aging, continues to study potential risk and protective factors such as menopausal hormone therapy and treatment of hypertension.
- The ongoing Age, Gene/Environment Study (AGES), conducted by the NIA Intramural Research Program in partnership with the Icelandic Heart Association, seeks to identify genetic and environmental factors involved in cognitive decline/dementia and an array of other age-related health conditions.
- The Health and Retirement Study (HRS) is genotyping approximately 20,000 participants and will use these data to elucidate genetic influence on a number of parameters, including cognition. HRS is/has recruiting/ed additional minority participants, further strengthening the study's utility in identifying risk and protective factors in these populations.
- The Alzheimer's Disease Genetics Consortium (ADGC) collaborates with the 29 NIA-supported Alzheimer's Disease Centers to conduct large-scale genome wide association studies (GWAS) in search of risk factor genes for the disease. The ADGC has leveraged a variety of existing epidemiologic, case-control, and family based data and sample sets, including African American and Hispanic cohorts.
- The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium facilitates GWAS meta-analyses and replication opportunities involving a number of NIH-supported studies, including AGES, the Framingham Heart Study, and

several others. Studies related to AD and cognition are included among the Consortium's efforts.

Additional NIA-supported research aimed at elucidating risk and protective factors among vulnerable populations includes the following:

- In an ongoing study, researchers are working to identify genetic risk factors for Alzheimer's disease (AD) in a cohort of Hispanics of Caribbean descent.
- The Chicago Health and Aging project is exploring several genetic and other risk factors for cognitive decline and AD in African American and non-Hispanic white participants, including the intersection of markers of inflammation, blood pressure, and other vascular factors with cognitive function.
- A recently completed study, initiated with funding from ARRA, assessed the associations of over 900,000 genetic markers with cognitive decline among 7,750 older African Americans and Africans.

Item

Biology of Aging. - The Committee applauds NIA's leadership role in the Geroscience Interest Group, which will promote coordinated discussion and coordination across NIH on research to reduce the burden of age-related disease. (p. 90)

Action taken or to be taken

The NIH Geroscience Interest Group (GSIG) was formed to accelerate and coordinate efforts to promote further discoveries on the common risks and mechanisms behind age-related diseases and conditions by developing a collaborative framework that includes multiple NIH Institutes and Centers (IC). By pooling resources and expertise, the GSIG identifies major cross-cutting areas of research and proposes coordinated approaches to identify hurdles and envision solutions.

In addition to conducting cross-institute informational activities such as seminars and other activities, one of the GSIG's principal goals is to develop trans-NIH initiatives, including Program Announcements (PA), Request for Applications (RFA), and other suitable mechanisms. The model initially being used to achieve these collaborations is identification of relevant topics through discussion by the Executive Committee, followed by prioritization and organization of workshops to canvass the researchers in the outside community. If the workshop leads to positive feedback, then an RFA (or other mechanism) will be developed by a lead IC with assistance from members from other ICs interested in the topic. For example, on September 6-7, 2012, the GSIG sponsored a workshop on inflammation and age-related diseases. It is anticipated that this activity might lead to an RFA on the subject, co-sponsored by several NIH ICs, pending the recommendations of the workshop. As a way of gaining further input from the research community, a larger-scale workshop tentatively entitled "Geroscience: Foundations for Delaying Chronic Disease and Increasing Healthspan" is planned for fall 2013. Another approach involves expansion of current IC RFAs to incorporate aims related to aging and health. For example, the scope of an ongoing RFA from NIAID on regeneration of the thymus -- an organ whose function decreases dramatically with aging, likely leading to a decrease in immune

response -- will be expanded to solicit applications for studies related to immune function in older individuals.

Item

Cognitive Interventions. - The Committee encourages NIA to continue support of studies to identify environmental, behavioral, and social factors that could protect against age-related cognitive decline as well as randomized studies to test the efficacy of behavioral and social interventions to slow or reverse age-related cognitive decline. (p. 91)

Action taken or to be taken

NIA supports a number of studies to identify environmental, behavioral, and social factors that could protect against age-related cognitive decline. Higher levels of exercise and physical activity, increased social engagement, a healthy diet, and mentally stimulating activities have all been associated with reduced risk of cognitive decline at older ages, although no causal link has been established. In a recent study, NIH-supported investigators studying older populations in the U.S., England, and 11 European countries found that early retirement (prior to age 65) was associated with a significant decline in cognitive performance. The investigators suggest that this may be in part because for many people retirement leads to a less stimulating daily environment, and the prospect of retirement reduces the incentive to engage in mentally stimulating activities on the job. Although further study is necessary, these findings suggest that the recent trend of American workers delaying retirement may eventually lead to improved cognitive performance in this group.

In addition, NIH supports randomized studies to test several behavioral and social interventions to slow or reduce age-related cognitive decline. For example:

- The Synapse Study compares the effects of a cognitive enrichment program (digital photography or quilting), a social enrichment program, physical exercise, and no intervention on cognition in older people.
- An ongoing project explores the cognitive effects of participation in Senior Odyssey, a collaborative problem-solving venture modeled on the children's educational program Odyssey of the Mind.
- Several studies directly test the effects of regular aerobic exercise on cognition.
- The Lifestyle Interventions and Independence for Elders (LIFE) study, a Phase 3 multi-center randomized controlled trial comparing a moderate-intensity physical activity program to a successful aging health education program in 1,600 sedentary older adults, has assessment of cognitive benefits of exercise as a secondary aim.
- The Research Partnership in Cognitive Aging is a public-private effort to promote the study of brain function with age. Through it, research grants have been awarded to examine the neural and behavioral profiles of healthy cognitive aging and explore interventions that may prevent, reduce or reverse cognitive decline in older people. This partnership, led by NIA and the McKnight Brain Research Foundation, seeks ways to maintain cognitive health – the ability to think, learn and remember - well into old age.
- Six pilot clinical trials on a variety of cognitive interventions supported by a FY 2009 Request for Applications (RFA) will be completing their enrollment and analyses soon, and it

is hoped that one or more of these will prove promising enough to justify a larger scale field trial.

Item

Demographic Research. - The Committee recognizes NIA for supporting research on the demographic, economic, and social consequences of an aging population in the United States and worldwide. A premier example of this research is the Health and Retirement Study, a longitudinal survey of more than 26,000 Americans that is now being replicated in over 30 other countries. (p. 91)

Action taken or to be taken

In FY 2012, NIH renewed funding for the Health and Retirement Study (HRS), which consists of a biennial collection of data from a nationally representative, population-based sample of over 26,000 Americans aged 50+ and their spouses. Ten waves of data have been collected since 1992, and an eleventh wave of data collection is under way. Recently, additional support facilitated doubling of the minority sample. HRS data are an important resource for researchers, students, and other government agencies: Over 2,220 scientific publications have resulted from the HRS, and the number of registered users of HRS data continues to increase.

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 national studies are ongoing in England, Ireland, China, South Korea, Mexico, and Japan and on the European continent; India has recently begun development of a study. Nationally-funded studies have been initiated in a number of countries, including Scotland, Brazil, and Argentina. 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. 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.

HRS is/has genotyping/ed on approximately 20,000 participants. These genetic data will advance our understanding of how genetic, behavioral, and psychosocial factors affect the health and well-being of older Americans.

In addition to the HRS, NIA supports a robust portfolio of demographic and economic research, including studies to estimate the economic consequences of aging and disability; research on the consequences of changes in the American family on old-age support; and cutting-edge studies on the biodemography of aging. Ongoing initiatives include:

- **Centers on the Demography and Economics of Aging.** NIH currently supports fourteen Centers on the Demography and Economics of Aging, which investigate aspects of health and health care, the societal impact of population aging, and the economic and social circumstances of the elderly. The reach of these Centers is global, with almost all involved in international projects.

- **Studies of Old Age Disability Trends and Dynamics.** The National Health and Aging Trends Study (NHATS) replaced the National Long-Term Care Survey as the source of research data on national disability trends and dynamics among the US older population. NHATS completed its baseline wave of data collection in October 2011; the baseline data became publicly available to the research community in the Spring of 2012.
- **Studies of Behavioral Economics and Neuroeconomics.** Research integrating insights from the fields of psychology and neuroscience is enhancing our understanding of how older persons make important economic decisions about savings, adherence to medical treatment, and health behaviors. NIH supports a number of projects that examine social and economic behaviors of relevance to aging, using approaches that examine mechanisms and processes at the social, behavioral or psychological level, as well as the neurobiological or genetic level.

Item

Measurement of Well-Being. - The Committee commends NIA for working with the Economic and Social Research Council in Great Britain to develop subjective measures of well-being as a complement to objective health measures and traditional economic indicators of progress. The Committee encourages the continued development of these metrics and their incorporation into national surveys. (p. 91)

Action taken or to be taken

Development of valid measures of subjective well-being (including pain and suffering) and incorporation of those measures into large surveys remain priorities for NIA. For example, the Roybal Center for Translational Research on Aging at Princeton University focuses on development and use of measures of well-being. Roybal investigators have developed and tested several new instruments, and considerable headway has been made introducing these instruments to the scientific community. NIH-supported pilot studies are also ongoing that incorporate brief measures based on the Day Reconstruction Method, which integrates assessment of mood and behavior with a detailed time diary of the day's activities, into studies associated with the Health and Retirement Study. These measures are also being incorporated in several other national cohort studies such as the English Longitudinal Study.

In addition, in 2011 NIA released a research solicitation for projects to advance our understanding from both individual and population perspectives of how age, health status, employment status, or other aging-relevant life circumstances or stages impact the various components of subjective well-being. Six grants were awarded, including:

- A study of the use of self-reports as measures of well-being, incorporating an investigation of the role of religiosity in well-being;
- A comprehensive analysis of measures of well-being currently used across populations and countries;
- A study of how well-being evolves over the life course; and
- A study to develop brief but valid and comprehensive measures of subjective well-being for incorporation into large surveys.

NIA looks forward to a continued productive partnership with the UK Economic and Social Research Council (ESRC). In 2010, NIA and the ESRC co-sponsored a National Academy of Sciences (NAS) workshop on the policy potential and implications of well-being metrics. At this meeting, consensus emerged that subjective wellbeing measures could be useful and appropriate for targeted populations and targeted policies, but questions remained regarding their potential to capture meaningful information from societies at large. Currently an NIA and ESRC funded NAS Panel on Measuring Subjective Well-Being in a Policy Relevant Framework is in place and is attended by representatives of several federal statistical agencies.

In November 2011, NIA and the Brookings Institution followed that workshop with another workshop on “The Use of Well-Being Measures in Policy Analysis,” in which ESRC members participated. The group concluded that facilitating the inclusion of metrics of subjective well-being into policy design and analysis is an important research priority and identified a number of key next steps.

Item

Neuropsychology and Alzheimer’s. - Recognizing that neuropsychological assessment can provide detailed information about cognitive deficits related to dementia or trauma, the Committee encourages NIA to continue research that links neuropsychological markers with Alzheimer’s biomarkers. (p. 91)

Action taken or to be taken

Neuropsychological assessment remains a cornerstone of the diagnosis of neurological disease. In September 2012, the NIH Toolbox for Assessment of Behavioral and Neurological Function was introduced to the research community.¹ The NIH Toolbox is a set of brief measures assessing cognitive, emotional, motor and sensory function from ages 3-85, providing a standard set of measures that can be used as a “common currency” across diverse study designs and settings. The NIH Toolbox enables monitoring neurological and behavioral function over time, which facilitates the study of functional changes across the lifespan, including evaluating intervention and treatment effectiveness.

In addition, NIA has made significant progress in linking neuropsychological markers with fluid and imaging biomarkers in Alzheimer’s disease (AD). For example:

- In two separate studies, NIH-supported investigators found that higher amounts of beta-amyloid in the brains of dementia-free people were associated with an increased risk of developing dementia over time as well as with subtle declines in cognitive abilities and loss of brain volume. These findings suggest that brain beta-amyloid may in fact be a preclinical sign of disease even among individuals who appear cognitively normal.
- Researchers with the NIH-supported Alzheimer’s Disease Neuroimaging Initiative established a method and standard of testing levels of both *tau* and beta-amyloid proteins, known biomarkers for AD in the cerebrospinal fluid (CSF). They correlated levels of these proteins in the CSF with changes in cognition over time and determined that changes in these

¹ The NIH Toolbox for Assessment of Behavioral and Neurological Function can be accessed at <http://www.neuroscienceblueprint.nih.gov/factSheet/toolbox.htm>.

two protein levels in the CSF may signal the onset of mild AD. These and other findings have facilitated the first revision of the clinical diagnostic criteria for AD in 27 years through a joint effort of NIA and the Alzheimer's Association. Among other things, the new guidelines address the use of imaging and biomarkers to determine whether changes in the brain and body fluids are due to AD.

- The NIA-supported Harvard Aging Brain Study is designed to elucidate the impact of amyloid on the aging brain and to determine the factors that predict successful cognitive aging and cognitive decline towards mild cognitive impairment (MCI) and AD dementia. Early results suggest that high amyloid burden in cognitively normal older individuals is associated with brain imaging abnormalities consistent with those seen in MCI and AD. A longitudinal clinical follow-up will help determine whether these individuals are indeed in the preclinical stages of AD.
- Phase two of the Alzheimer's Disease Neuroimaging Initiative is now under way to define changes in brain structure and function as people transition from normal cognitive aging to MCI to AD. This effort will continue to track changes in the brain with both clinical and cognitive testing and brain scans measuring glucose metabolism and the amount of beta-amyloid protein deposited in the brain. Other studies, including the Alzheimer's Disease Cooperative Study, are focusing on new trial approaches using imaging and other biomarkers in cerebrospinal fluid and plasma to identify participants with AD pathology and to track disease progression and treatment response.

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

Senate Significant Items

Item

Heritable Connective Tissue Disorders. - The Committee encourages NIAMS to expand its collaborative efforts with other Institutes to support clinical and translational research aimed at identifying effective therapies for heritable connective tissue disorders, particularly Marfan syndrome. (p. 91)

Action taken or to be taken

Heritable disorders of connective tissue strike the body's foundation. They are characterized by defects in genes encoding proteins of the extracellular matrix that serves as connective tissue in holding the body together and providing a framework for growth and development. Mutations in the gene for fibrillin, a ubiquitous extracellular matrix protein, are the basis for many rare, yet often severe, inherited diseases that primarily strike children or young adults.

In Marfan syndrome, the connective tissue found throughout the body is abnormal, affecting many body systems adversely, including the skeleton, eyes, heart and blood vessels, nervous system, skin, and lungs. In some cases, the complications are life threatening. Marfan patients often have elongated bones, above-average height, and cardiovascular problems. 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. More recently, scientists funded by NIAMS found that a key regulator of connective tissue structures, called transforming growth factor beta (TGF- β), may contribute to their malfunction in Marfan syndrome.

In contrast, preliminary studies suggest that a different fibrillin gene mutation in Weill-Marchesani syndrome does not involve TGF- β ; instead, the fibrillin protein loses its ability to interact with molecules that maintain the connective tissue environment. As a result, Weill-Marchesani patients have physical characteristics that are very different from Marfan patients: shorter stature, thick skin, stubby fingers, and eye problems, which can lead to blindness. Recent discoveries have linked additional fibrillin gene mutations to two conditions that also involve bones, joints, skin, and the cardiovascular system; these conditions are usually fatal in early childhood. This new knowledge furthers our understanding of the molecular pathogenesis in these disorders and reveals potential new drug targets for their treatment.

NIAMS continues to support a broad portfolio of connective tissue biology and musculoskeletal research that is relevant to Marfan syndrome, including co-funding, with the National Heart, Lung, and Blood Institute (NHLBI), the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). Advances and resources from these programs will enable further Marfan research and, ultimately, improve the clinical management of complications from Marfan syndrome and the quality of life of patients. NIAMS encourages Marfan investigators to engage colleagues within the fields of connective tissue and

musculoskeletal biology in order to explore new areas of research and collaborations focused on the musculoskeletal manifestations of the disease.

Item

Osteogenesis Imperfecta [OI]. - The Committee urges NIAMS to support natural history studies of OI that will facilitate efforts by advocacy groups and medical professional societies to develop clinical practice guidelines for adults living with OI and to increase research on emerging issues. The Committee encourages NIAMS to work with relevant stakeholders from government, medical professional societies, and advocacy groups on this matter and to provide an update in the fiscal year 2014 congressional budget justification. (p. 91)

Action taken or to be taken

NIAMS supports a broad portfolio of bone biology and musculoskeletal research that is relevant to Osteogenesis Imperfecta (OI). Advances in these programs help to inform the field and, ultimately, improve the quality of life of patients. As part of an effort to raise awareness about OI clinical research, NIAMS specifically mentioned OI in a FY 2012 initiative to encourage small businesses to conduct research that could lead to biomarkers or therapies for rare diseases. NIAMS also funds research aimed at applying the tools of genetic and stem cell technology to develop therapies that could correct the underlying genetic defects in OI.

In 2012, NIAMS partnered with the National Institute on Deafness and Other Communication Disorders (NIDCD) and the National Center for Advancing Translational Sciences (NCATS) to provide grant support for an Osteogenesis Imperfecta Foundation, Inc., conference titled *Assessing the Impact of Osteogenesis Imperfecta on Non-Skeletal Systems*. The meeting brought together leading OI researchers and clinicians, as well as adults living with the disease, to review knowledge about the impact of OI on a range of bodily systems as patients age, and identify major information needs. Conference organizers have agreed to share insights gained at the conference with a wider audience through venues such as the OI Foundation website, the OI Foundation newsletter, and submission of a workshop report to a peer-reviewed journal.

NIAMS uses other strategies, in addition to conference grants, to work with stakeholders to encourage research that will improve the lives of people who have OI. The Institute leads the Federal Working Group on Bone Diseases, which offers a forum for federal agencies and others who are interested in collaborative bone research activities—including emerging research opportunities related to rare bone diseases such as OI—to exchange information and coordinate their efforts. NIAMS is participating in two funding opportunity announcements, led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), to encourage studies that will establish an evidence base for health promotion strategies related to physical activity and diet for children who have physical disabilities. OI is one of the conditions noted in the solicitations.

Like NIAMS, NICHD supports a range of basic, translational, and clinical research on OI. In response to a funding opportunity announcement soliciting research on the causes of birth defects, NICHD recently funded a program project grant on how OI develops, testing the theory that mutations that produce OI may result from a convergence of cell defects. Scientists working

in NICHD-funded laboratories are examining mouse models of OI to better understand the mechanisms of the disease and to identify new genes that cause recessive forms of OI. They are also collaborating with University of Michigan investigators to explore the effects of a new antibody on the bones of the mouse model. The NICHD intramural program focuses on clinical studies for pediatric patients, including an ongoing study on the pulmonary, cardiac, auditory, and neurological complications of OI. Recently published data from this research demonstrated the decline of pulmonary function and early onset of cardiac valve problems in children with OI; the study will serve as the basis for the development of early interventions to prevent or delay these complications.

Item

Scleroderma. - The Committee continues to be pleased with the progress of the Institute as it relates to scleroderma. The Committee encourages NIAMS to concentrate efforts on identifying genetic components that increase the likelihood of developing this disease. (p. 91)

Action taken or to be taken

Scleroderma is a group of autoimmune diseases involving abnormal growth of connective tissue often manifested as hard, tight skin. However, in some individuals this disease may also affect blood vessels and internal organs (e.g., heart, lungs, and kidneys), often leading to profound disability and premature death. This form of scleroderma, known as systemic sclerosis (SSc), is an important focus of current NIAMS funding. Understanding the genetic factors that lead to the development of SSc is a fundamental step toward effective treatments and potential cures.

A new NIAMS Center of Research Translation (CORT) is investigating genetic biomarkers of SSc at Boston University. CORTs encompass a multidisciplinary approach and are made up of at least one basic and one clinical project. The highly interactive, patient-oriented studies included in this project are designed to coordinate the work of numerous scientists and clinicians to accelerate understanding of the disease process. In addition, a NIAMS-supported Rheumatic Diseases Core Center has been created to provide common resources and platforms for high technology analyses to SSc investigators. This coordinating effort, also located at Boston University, will help advance research in SSc by making tissue samples and state-of-the-art analytical processes available to a wide range of scientists throughout the U.S. Finally, the roles of genetic variants in SSc are being explored by a newly funded NIAMS Multidisciplinary Clinical Research Center (MCRC) in Rheumatology at Northwestern University. MCRCs focus on assessment and improvement of clinical outcomes for patients.

Mice with the thick-skin 2 mutation (Tsk2) display many of the features of human SSc, including tight skin and significant autoimmunity, as well as abnormalities in the extracellular matrix. While it is known that the Tsk2 mutation is involved in SSc, the specific gene for this mutation has not yet been identified. NIAMS-supported researchers are studying this mouse model to identify the gene and ascertain how it leads to the development of SSc. The results of this research may help identify new targets for treatment of SSc in humans.

Researchers funded by NIAMS are looking for new methods of associating specific gene “signatures” with various clinical phenotypes of SSc. Archived frozen tissue samples from

patients with SSc are not suitable for DNA microarray analysis, and fresh frozen tissue samples are difficult to obtain, due to the rarity of SSc. This project seeks to compare two different methods of genomic analysis on archived and fresh-frozen tissue samples, and use one of these methods to test a larger number of samples. This will greatly increase the genomic database, which in turn may lead to new insights into SSc and potentially the development of new therapies for its various subtypes.

NIAMS has also supported research by scientists who recently identified a peptide dubbed E4. In laboratory tests on human skin tissue, this peptide protected against the development of fibrosis, a thickening of the skin or internal organs, which is a potentially fatal characteristic of diseases like scleroderma. The eventual goal of this research is the development of therapies that will prevent or reverse fibrosis and preserve organ function.

Item

Temporomandibular Disorders [TMD]. - Many people who have TMD suffer from conditions that routinely affect other joints in the body, such as trauma, arthritis, and fibromyalgia. Therefore, the Committee calls on NIAMS to collaborate with NIDCR and NIBIB to bring the intellectual and scientific resources within these Institutes to the study of 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 jaw pain and dysfunction. (p. 91-92)

Action taken or to be taken

Temporomandibular joint disorders (TMJD) are a group of conditions that cause pain and dysfunction in the jaw joint and muscles that control jaw movement. In addition to the many NIAMS-funded projects related to joint physiology and arthritis, NIAMS supports a range of basic, translational and clinical studies on fibromyalgia and other chronic pain conditions that could help to inform the TMJD community.

Several of these projects were funded in direct response to a series of funding opportunity announcements in which NIAMS and other NIH Institutes and Centers are participating. Examples of NIAMS-funded projects include efforts to identify genetic, systemic and experiential factors (for example, race-based discrimination) that influence the development of chronic pain after trauma suffered during motor-vehicle collisions. Because chronic pain conditions such as TMJD affect many more women than men, other scientific efforts are characterizing sex differences in the multiple mechanisms that people have to suppress pain. The role of urocortin (a naturally occurring protein that widens the blood vessels) in how people perceive musculoskeletal pain is another promising area of NIAMS-funded research that may be applicable to TMJD.

NIAMS continues to support research into the molecular basis of TMJD and inflammatory knee arthritis. One study is funded through the highly competitive Pathway to Independence award

that supports promising early-stage scientists as they transition from mentored postdoctoral positions to tenure-track, independent research careers. This investigator is developing an animal model of knee arthritis that can be adapted for future studies of problems related to TMJD, such as orofacial sensitivity, bite force, dietary habits, and sleep patterns.

Establishment of the NIAMS intramural Laboratory of Oral Connective Tissue and Biology is affording other opportunities for NIAMS and the National Institute of Dental and Craniofacial Research (NIDCR) researchers to interact. Led by NIDCR Director Dr. Martha Somerman, the lab complements the expertise of other NIAMS intramural laboratories and provides new opportunities for strategic collaborations to advance knowledge of hard and soft connective tissues of the jaw and other joints, as well as help identify links between systemic conditions and the oral cavity.

In addition to those efforts funded by NIAMS, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) supports research to engineer two different types of cartilage found in the articular disc (a plate in the TMJ that provides a cushion between bones) into a single implant that can be used to replace the disc. NIBIB also supports research on improving implanted devices such as developing coatings to reduce wear and erosion, important design considerations for small, articulating surfaces such as those seen in the TMJ. Also, while not specific to the TMJ, NIBIB supports two imaging projects to develop novel MRI approaches that are sensitive to early cartilage degradation. Standard MRI can track a substantial reduction in cartilage thickness, but the degradation is often irreversible by the time it is detected. If these novel approaches succeed in detecting early damage to cartilage, they may enable new methods to understanding the damage etiology or to treating cartilage degradation in the TMJ.

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National Institute on Deafness and Other Communication Disorders (NIDCD)

Senate Significant Items

Item

Clinical Trials for Human Communication Disorders. - The Committee encourages NIDCD to expand its clinical trials program and commends the Institute for a funding opportunity announcement that encourages industry collaboration and requires both clinical and basic scientists to be a part of research teams. (p. 92)

Action taken or to be taken

NIDCD's active clinical trials include studies on hearing aids, cochlear implants, and other interventions to address hearing impairment among children and adults that are caused by noise-induced hearing loss, otitis media, presbycusis, and tinnitus. Other active clinical trials address NIDCD's mission areas of voice, speech, and language.

NIDCD's extramural clinical trials program has grown considerably since 2008, when it issued three funding opportunity announcements for clinical trials in communication disorders. As a result of these announcements, grant applications involving clinical trials increased approximately three-fold over four years. To strengthen these applications, NIDCD's clinical trial funding mechanisms were converted to cooperative agreements in FY 2012, enabling NIDCD program officers to offer greater assistance in trial design, application, and execution. The extramural clinical trials program is expected to grow with the incorporation of the cooperative agreement mechanism and with its support for a new practice-based research network that will assist clinical trials and other clinical research. The use of cooperative agreements and the new network will enable NIDCD to promote collaborations between research teams when developing clinical trials.

NIDCD continues to foster and expand clinical studies and trials within its intramural research program. Ongoing clinical studies helped identify new genes and how they contribute to hereditary deafness, stuttering, and neoplasms that affect voice and speech. These studies may be useful in the development of new treatments. For example, clinical studies using brain imaging have defined how stroke affects speech and language and examined the effects of rehabilitative therapy. Clinical trials have included testing of a possible vaccine for otitis media. NIDCD intramural scientists are collaborating with scientists from the National Cancer Institute and the National Institute of Dental and Craniofacial Research on a trial to determine new molecular targeted agents for treatment of individuals with mouth and throat cancer. In addition, NIDCD hired two clinician scientists who are demonstrating the potential of exposing individuals to moderately loud sound or to certain drugs can activate protective responses in the ear to reduce hearing loss caused by antibiotics or chemotherapy drugs. Clinical trials such as these are vital to the pursuit of knowledge in addressing human communication disorders.

Item

Dementia and Hearing Loss. - The Committee recognizes the association of unaddressed hearing loss with pre-dementia and dementia and advocates investigating whether hearing loss is a cause for dementia, whether hearing-loss interventions will slow or halt dementia, and how rehabilitative interventions for hearing loss can be delivered in communities. (p. 92)

Action taken or to be taken

Dementia is a disorder affecting the mental abilities of the brain. People with dementia have difficulty with memory, problem-solving, and controlling their emotions, and eventually may lose the ability to do everyday life activities, including personal care tasks of getting dressed, bathing, and eating. The prevalence of dementia increases with age and is projected to affect 100 million people, or nearly one in 85 persons, worldwide by 2050. Age-related hearing loss (ARHL) affects an estimated 30 percent of adults aged 65-75 years and 47 percent of people 75 and older. Given the prevalence of both conditions, multiple studies are under way to observe hearing loss in individuals with cognitive decline and dementia.

Results from NIDCD-funded studies suggest that age-related hearing loss may be associated with accelerated cognitive decline in older individuals. A clinician-investigator supported by NIDCD is collaborating with a team of intramural scientists from the National Institute on Aging to study the association of hearing loss and dementia. They compared the baseline hearing levels of subjects from the Baltimore Longitudinal Study of Aging with the results of cognitive testing performed every two years over the period of more than a decade. Age-related hearing loss was found to be strongly associated with poor cognitive functioning and dementia. In individuals older than 60 years of age, more than one-third of the risk of dementia was associated with hearing loss. Compared with age-matched subjects with normal hearing, individuals with mild, moderate, or severe hearing loss have a two-, three-, or five-fold risk of developing dementia, respectively.

It is unclear whether the underlying relationship between hearing loss and dementia represents a cause-and-effect. Similarly, the base(s) of this association remain to be identified. It may be that social isolation related to age-related hearing loss can contribute to dementia. Another possibility is that a common disease process, such as vascular disease, may contribute to both hearing loss and dementia. Yet another possibility is the finding that during hearing loss, the brain allocates greater cognitive resources to auditory processing and communication, which may accelerate the appearance of dementia in the aging brain.

NIDCD is interested in establishing whether treating hearing loss with hearing aids and/or other forms of auditory rehabilitation could halt or slow cognitive decline and dementia in older adults. One randomized control trial conducted more than two decades ago demonstrated positive effects of hearing aids on cognitive and other health functions in a population of military veterans.

NIDCD's research program also supports projects to develop and disseminate interventions for hearing loss in community settings. In the last two years, NIDCD has issued a series of research initiatives seeking to enhance the access and affordability of hearing health care services to

adults with hearing loss. An important goal of these initiatives is to encourage research that leads to improving the delivery of hearing health care interventions to the community.

Item

Early Detection, Diagnosis, and Intervention. - The Committee urges NIDCD to continue research on the auditory, speech, language, voice, and psychosocial outcomes of children identified with hearing loss through newborn screening. Additionally, the Committee is aware of data that show a higher prevalence of hearing loss than thought among school-age children who passed newborn screening. Therefore, the Committee recommends more research on methods of screening for both mild hearing loss in infancy and for late-onset hearing loss. The Committee also encourages NIDCD to continue studying optimal sound amplification strategies for children's hearing aids, particularly to enhance speech recognition in noisy classrooms, and the effects of services and parental engagement on the emotional well-being of the hearing-impaired child. (p. 92)

Action taken or to be taken

Approximately two to three in every 1,000 children in the U.S. are born with severe to profound deafness. The implementation of universal newborn hearing screening, a joint effort by NIDCD and other federal agencies, has dramatically improved the identification of infants with hearing loss (HL) and accelerated the initiation of services for these children. Today, more than 95 percent of infants are screened for HL. NIDCD continues to examine the outcomes of children identified through newborn hearing screening.

In a NIDCD-supported multisite study, investigators are examining whether certain characteristics in children, their families, or interventions are associated with different functional outcomes in children ages two to six with mild to severe HL. This study identified that children with HL are at greater risk than normal hearing children of having difficulty with language structure and social cognition. This becomes increasingly important by fourth grade, when children must rely on reading comprehension to learn new material and adapt their social skills to a variety of situations. In another NIDCD-supported study, investigators are studying the communication, social-emotional, and adaptive functioning outcomes of children ages one to four with mild to severe HL. This study indicates that children with HL perform at the low range of normal on most measures for their age group. Other NIDCD-supported studies have found that young children with HL perform poorer than their normal hearing peers on measures of language competence. NIDCD continues to expand its research portfolio to study methods of screening for both mild HL in infancy and for late-onset HL.

The number of hearing-impaired children identified by newborn screening programs and receiving a cochlear implant prior to age two is increasing, and many of these children are participating in mainstream classrooms. However, hearing-impaired children remain 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 cochlear implants. NIDCD-supported scientists are examining the neurological bases of these variations to improve clinical management strategies. Scientists are also studying how cochlear implants and language experiences impact

cognitive and social functioning as cochlear-implanted children enter school. 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.

NIDCD-supported scientists are working to identify optimal sound amplification strategies for children with HL. 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, scientists are comparing the ability of extended frequency bandwidth hearing aids and frequency lowering hearing aids to capture high frequency components of speech. In addition, NIDCD is funding research on the psychosocial outcomes of children with mild to severe HL, including how parental engagement and support and services delivery affect the long-term emotional well-being of the child.

Item

Hair Cell Regeneration and Replacement. - The Committee continues to place a high priority on research involving cellular regeneration of the inner ear. The Committee advocates the goals to identify genes and factors that promote regeneration cited in the 2012–2016 NIDCD Strategic Plan for Research. (p. 92)

Action taken or to be taken

The NIDCD grant portfolio reflects the high priority NIDCD places on research directed at regenerating the hair cells of the inner ear and better understanding how stem cells give rise to the mature cell types of the inner ear. Scientists funded by NIDCD are using different animal models to learn how cells in the inner ear regenerate, and working to understand how regenerated cells establish connections with the brain.

One area of focus is on developing hair cell regeneration strategies. Scientists know that the supporting cells in the inner ears of chickens divide to regenerate lost hair cells, but this same phenomenon does not normally happen in mammals. A team of NIDCD-supported scientists identified a growth factor called EGFR that is vital for supporting cell division in chickens, and determined that adding EGFR to mouse inner ear-supporting cells in culture enables them to begin dividing again. They now hope to use this discovery to develop hair cell regeneration strategies for mammals. In related research, NIDCD intramural scientists found evidence that many non-sensory cells (including supporting cells) within the mouse inner ear retain the ability to develop as either hair cells or functional neurons. Forcing the cells to express specific factors that alter gene expression can redirect the fate of the cells. However, the non-sensory cells lose this ability as the animals mature, suggesting that similar changes in cell fate are probably not possible in adult inner ears. They are now working to understand why non-sensory cells lose their ability to respond to gene expression factors over time. Another NIDCD-supported team is working to convert mouse embryonic stem cells (mESCs) into inner ear hair cells. They plan to use these mESC-derived hair cells to treat a mouse model of inherited deafness.

Scientists know that too much loud noise can damage the nerve cells that carry sound information from the hair cells into the brain. Although these nerve cells regenerate and

establish synapses (connections) with the hair cells in the cochlea, a snail-shaped structure in the inner ear that contains the organ of hearing, the new synapses are not always as mature and functional as before damage. Often the synapses are fewer in number, and each new nerve cell frequently connects with more than one hair cell, instead of the normal one-to-one ratio. NIDCD-supported scientists have developed a culture system to study regeneration of synapses following damage, and are testing the ability of different growth factors to improve the quality and quantity of regenerated synapses. Another NIDCD-supported scientist is testing drugs to improve synapse regeneration in the vestibular (balance) system of the inner ear. A third team of NIDCD-supported scientists used gerbils to demonstrate that nerve cells that develop from transplanted stem cells can re-innervate hair cells of the inner ear after the normal nerve cell connections are destroyed. They are now working to understand what characteristics of the nerve cells formed from the transplanted stem cells enable them to form functional synapses with hair cells. They are also investigating whether the new synapses lead to recovery of hearing in animals where the normal connections degenerate. The scientists hope that improvements in our ability to regenerate these nerve cells and their synapses with hair cells will lead to new treatments for hearing loss.

Item

Hearing Aids and Cochlear Implants. - The Committee encourages additional research that compares the benefits of high- and lower-cost hearing aids, creates screening protocols for hearing loss in primary care settings, and continues collaborations between industry, scientists, clinicians, and consumers in the area of low-cost hearing aids. The Committee recommends further studies of the relationship between the success of hearing aid fittings and the cognitive capabilities of the hearing aid user, and supports further development of an automated hearing-screening kiosk. The Committee is pleased that NIDCD is funding cochlear implant research for those with severe-to-profound hearing loss and recommends additional studies on new electrode design and innovative approaches to speech processing. The Committee further urges continued research into studies evaluating and comparing the benefits of the “bimodal” option of an implant in one ear and a hearing aid in the other, and of a middle ear implantable device that combines electromechanical and acoustical stimulation in the same ear. The Committee encourages NIDCD to continue to monitor cochlear-implanted children as they enter school, including their development of higher-order cognitive and language skills, speech production and recognition, and behavioral and social adjustment. (p. 92-93)

Action taken or to be taken

For the 36 million American adults who report having some degree of hearing loss, the hearing aid is the primary device available for managing hearing loss. However, adoption is often slow; even among those who use hearing aids, most people live with hearing loss that has progressed to moderate-to-severe levels. NIDCD has promoted research collaborations to improve the accessibility, affordability, and outcomes of hearing health care. In response to these initiatives, NIDCD-supported scientists are examining several aspects of hearing aid outcomes, as well as service delivery, screening, and follow-up methods, with the goal of increasing access to effective, lower cost, hearing health care for underserved older adults. In addition, NIDCD-supported researchers are developing and testing an automated hearing screening kiosk designed

to motivate those who fail screening 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 is an important tool for managing severe-to-profound hearing loss. It is the most widely utilized neural prosthetic device worldwide. NIDCD has supported the design, construction, and distribution of a research interface that works with some commercially available cochlear implants. This interface is battery operated and portable, making it possible to evaluate user performance. The interface will be used to test novel speech processing strategies in implanted individuals under an Investigational Device Exemption provided by FDA. NIDCD has partnered with the Department of Energy (DOE) to use a dedicated clean room facility and construct novel electrode arrays. Although these devices will be used in animal studies initially, the unique arrangement with the DOE thereby lowers barriers to manufacturing devices suitable for human use.

Recently, NIDCD-supported scientists investigated ways to improve the selection and fitting of cochlear implants to severely hearing-impaired individuals with predominantly high frequency hearing loss and residual low frequency hearing in the better ear. Research in both adults and children is under way to evaluate the “bimodal” fitting alternative (cochlear implant and contralateral acoustic hearing) and compare it to the electrical and acoustical stimulation (EAS) of the same ear through implanting a short electrode (cochlear implant and binaural acoustic 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 for both adults and children.

NIDCD-supported investigators are also examining variables that may influence language learning after implantation, including environmental, social, interventional, and biological influences. Variables include oral language and literacy skills, speech production, speech recognition, cognitive skills, social interaction & behavior, relationships with family members, and health-related quality of life. Researchers hope that this prospective, multisite, multidimensional study will provide novel, generalizable insights into the sources of variation in oral language learning after cochlear implantation in childhood.

Item

Hearing Impairment Among Children and Young Adults. - The Committee urges additional research on children and young adults with mild and unilateral hearing loss from all modes of injury. In particular, the Committee recommends further studies on this group’s diminished educational outcomes and development of strategies to improve school achievement. The Committee commends NIDCD for “It’s a Noisy Planet!”, a public education effort in English and Spanish about the dangers of hearing loss from noise exposure. The Committee also encourages NIDCD to continue to explore new ways to engage and broaden audiences through social media. (p. 93)

Action taken or to be taken

Up to one in 20 school-aged children in the U.S. has a unilateral hearing loss (UHL). 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. More recent work from this group suggests that children with UHL have deficits in processing speech sound and in working memory functions such as language comprehension and learning.

NIDCD-supported scientists use functional imaging technology to study the brain organization and auditory processing abilities of children with UHL. Results from this research indicate that UHL affects the organization of the brain and limits the ways in which auditory processing tasks are accomplished. For instance, normally developing connections used in comprehending the meaning of speech may be disrupted in children with UHL. Understanding the differences between hearing children and children with UHL may help inform the development of interventions to minimize the risk of children with UHL experiencing diminished educational outcomes.

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). Towards this goal, NIDCD continues to promote early education about NIHL and its prevention in elementary and middle-school children through the *It's a Noisy Planet. Protect their Hearing* campaign. This campaign brings the message of hearing health and hearing protection into classrooms and homes using fun interactive presentations, websites, and brochures.

In the past year, the campaign has expanded its efforts to more broadly reach parents of tweens (ages 8 to 12 years), educators, and health professionals through traditional and new media channels as well as through partnerships with advocacy groups and professional societies. In 2011, NIDCD released a series of English and Spanish radio and print public service announcements, potentially reaching more than 70 million people across the country.

NIDCD also utilizes social media to increase engagement with the public. A Facebook page for the campaign was established in 2011 and serves to expand reach to parents, educators, and health professionals. NIDCD now posts daily to the page, engaging fans with quizzes, news, videos, events, and tips on how to teach tweens about the dangers of loud sounds. There are currently hundreds of Noisy Planet fans. NIHL in children and the Noisy Planet campaign are among the most popular topics posted from the NIDCD Twitter handle, which also promotes research and other public health messages relevant to NIDCD. English and Spanish tweets leading users to Noisy Planet's interactive sound ruler were among our most retweeted posts, reaching nearly 6,000 Twitter users in addition to our 500 followers.

Future campaign activities include expanding partner activities, adding content and interactive tools for parents, and building capacity for partner organizations and others to provide in-person educational sessions to tweens about hearing health and preventing NIHL.

Item

Hereditary Hearing Impairment. - 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. 93)

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. Using technologies like targeted genomic capture and massively parallel sequencing, these scientists 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 alleles in 20 additional deaf individuals and their families. A team of NIDCD intramural scientists identified TPRN as a novel gene for nonsyndromic deafness, which is hearing loss or deafness not associated with other inherited clinical characteristics. Mutations of TPRN disrupt the encoding of taperin –a protein essential to the function of tiny hair-like projections found on hair cells in the inner ear that help transform sound energy into electrical energy. A second team of NIDCD intramural scientists discovered that mutations in the GIPC3 gene cause one form of adult-onset hearing loss by encoding hair cell proteins that are less stable and break down quickly. Scientists are now working to describe the functions of proteins encoded by the identified deafness genes to further our understanding of the biological mechanisms involved in hearing loss.

NIDCD-supported scientists are also working to understand the genetics of stuttering. A team of intramural scientists focused on families with many cases of stuttering that persist beyond childhood. They identified the locations of a number of causative genes on different chromosomes, and in some cases were able to identify the responsible gene. Although the genes identified thus far are responsible for a small fraction of stuttering, they provide new insights into the cellular and molecular causes of stuttering. The team is now actively working to identify additional genes to explain the causes of stuttering, and collectively account for a larger fraction of this communication disorder.

Another team of NIDCD intramural scientists is working to describe the location and probable function of myosins, which are proteins within the sound-conducting structures of the ear. Their research is helping them develop hypotheses about the causes of deafness and hearing loss when an individual inherits a gene that makes a mutant myosin protein, such as in late-onset hearing loss or in Usher syndrome, a disorder resulting in deafness and blindness.

NIDCD is supporting the 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. It will also help healthcare professionals identify children 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 translate basic research findings into clinical tools, such as a project to make comprehensive genetic testing for deafness available to clinicians

for under \$500 per person. This will enable healthcare providers to use genetic screening as a diagnostic test for deafness, following medical history and physical exam.

Item

Noise-Induced and Environmental Hearing Loss. - The Committee continues to encourage NIDCD to promote public awareness of the importance of protecting hearing from noise, through public service announcements or other means. The Committee also encourages studies in normal-hearing children of the impact of noisy classrooms on learning, continuation of a study measuring hearing thresholds and noise exposure levels in 18- to 25-year-olds, and environmental and genetic research into factors that predispose individuals to noise-induced hearing loss. (p. 93)

Action taken or to be taken

Preventing and treating noise-induced hearing loss (NIHL) is a priority for NIDCD. Prevention of noise-induced hearing loss would improve quality of life for the millions exposed to excessive noise, and decrease healthcare costs for individuals, businesses, and government agencies. Promoting public awareness of the importance of protecting hearing from excessive noise and communicating effective measures to prevent NIHL is essential to improving the hearing health of the U.S. population. NIDCD uses a variety of methods to increase public awareness, including traditional media channels. NIDCD's public education campaign to prevent NIHL, *It's a Noisy Planet. Protect Their Hearing*, targets parents of tweens (ages 8 to 12 years) and is produced in both English and Spanish. In July 2012, Noisy Planet was featured as a category on the national television game show *Jeopardy!* in a special Kids' Week episode, with viewership of more than five million people.

In 2011, NIDCD released a series of English and Spanish radio public service announcements about NIHL, and in the past year, NIDCD began employing social media to expand its reach and increase public engagement. NIDCD's Facebook page serves as a key channel to reach parents, educators, and health professionals. In addition, the NIDCD Twitter handle is used to promote relevant research and public health messages. Future campaign activities include expanding partner activities, adding content and interactive tools for parents, and building capacity for partner organizations and others to provide in-person educational sessions to tweens about hearing health and preventing NIHL.

NIDCD continues to support research to better understand the effects of NIHL as well as to identify risk factors. To understand the variability in susceptibility to NIHL and identify factors that may predispose people to develop NIHL, NIDCD-supported scientists are measuring hearing thresholds and noise exposure levels of 1,000 young adults between 18 and 25 years of age. The scientists will also examine participants for several genetic variations associated with NIHL to determine whether there are gene-environment interactions that contribute to NIHL.

NIDCD supported scientists are using animal models to examine the effects of non-traumatic levels of noise exposure on the cellular architecture of auditory hair cells and the neurons that connect them to the central nervous system. These studies will help scientists ascertain whether such exposures can progress, or predispose individuals, to NIHL.

NIDCD-supported scientists are also examining the use of antioxidants and other micronutrients to protect against NIHL. For example, 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. Scientists are also exploring the ability of an antioxidant to prevent blast-wave NIHL, a significant medical concern for military personnel. Other scientists are examining the use of a combination of FDA-approved drugs for the treatment and prevention of NIHL in animals. Finally, in an NIDCD-supported clinical trial, scientists are investigating the effectiveness of administering antioxidants with a vasodilator (a substance that widens blood vessels) in reducing or preventing NIHL following exposure to loud music or loud noise associated with military training exercises.

Item

Otitis Media. - The Committee supports continuing studies to develop new treatments for chronic and recurrent otitis media (ear infections), including treatment via a trans-tympanic antibiotic gel and prevention through intranasal vaccines. (p. 93)

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 problems spread to the middle ear. NIDCD supports several projects on the cause of OM. For example, NIDCD-supported scientists are examining how the bacterium *Streptococcus pneumoniae*, a leading cause of OM, colonizes the normal middle-ear flora. This study will aid in the development of therapeutics, provide information relevant to the control of other bacterial pathogens that colonize the respiratory tract, and 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, and whether environmental factors could reduce OM risks in children with genetic predisposition. NIDCD also supports research on the delivery of drugs to the middle ear, such as one project to develop an antibiotic gel that is applied once in the outer ear. Chemicals in the gel 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 that seek to develop vaccines against OM. NIDCD-supported scientists are evaluating how well two novel *Streptococcus pneumoniae* vaccines work to prevent OM and may be developed into an effective intranasal vaccine. In addition, NIDCD-supported scientists are developing non-invasive vaccines (e.g., transcutaneous or across the skin) to prevent middle ear infections aimed to target nontypeable *Haemophilus influenzae* (NTHi) and

the biofilms (sturdy bacterial structure that attacks respiratory tissue and is resistant to immune defenses) the bacteria produces.

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 establishment of the NIDCD Otopathology Research Collaboration Network and NIDCD's National Temporal Bone, Hearing and Balance Pathology Resource Registry to disseminate information about temporal bone donation. (p. 93)

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 65–74 years old and nearly 75 percent of people age 75 and older have hearing loss. NIDCD considers presbycusis an area of great importance and supports research on the complex interaction of inherited genes and environmental exposures that lead to presbycusis.

NIDCD continues to support the multidisciplinary Specialized Center on Experimental and Clinical Studies of Presbycusis, which aims to improve diagnostic, rehabilitative, and preventive measures for presbycusis. One reason that individuals don't use their hearing aids is their aids' inability to help them distinguish speech from noise. Scientists at the Center are currently studying how individuals understand speech and describing the actual benefit older adults gain by using hearing aids in realistic listening environments. They are using this information to modify amplification settings to provide an increase in hearing-aid benefit in real-life situations.

Recent animal model studies indicated that caloric restriction, which reduces oxidative stress to cellular components, may delay the onset of presbycusis. NIDCD is supporting a study examining the molecular basis for this effect in order to determine whether protecting the inner ear from oxidative stress may slow presbycusis. Additional NIDCD-funded studies are looking at the role of mitochondria in caloric restriction-mediated prevention of presbycusis and testing the ability of two FDA-approved drugs to prevent presbycusis in animal models. Such studies have the potential of providing the foundation for future preventative therapies. Another mouse study suggests that in older mice, signals from the brain's cortex that tell the thalamus to pay less attention to some sounds are decreased, which is likely to make it more difficult for the aging brain to focus attention to one sound in a noisy environment.

Scientists are also studying human temporal bones, which house the inner ear, in order to understand how their shape and function changes as a result of presbycusis or other human inner ear diseases. NIDCD funds the NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry to disseminate information about temporal bone donation and to enroll donors. NIDCD also supports temporal bone laboratories that act as both tissue banks and research laboratories. 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. 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. One Network lab has already identified 26 proteins uniquely associated with otosclerosis, a factor that contributes to presbycusis.

Item

Salt Intake and Salt Substitute. - The Committee encourages NIDCD to study whether taste perception will change following reduced salt intake and to determine the biological mechanisms of salt-taste transduction. (p. 93)

Action taken or to be taken

Approximately 32 percent of American adults have hypertension, a condition that increases the risk of numerous serious health conditions, including heart disease, kidney failure, and stroke. Hypertension is strongly associated with the excess consumption of salt, which is driven by its culinary desirability and its frequent addition to processed foods. In the 2012-2016 NIDCD Strategic Plan for Research, the overconsumption of salt is identified as an area of particular concern, with emphasis placed on the development of novel approaches to reduce salt in foods, while maintaining palatability.

NIDCD-supported studies address mechanisms by which salt is recognized by taste cells and how this information is conveyed to the brain. NIDCD-supported scientists are developing novel functional imaging and electrophysiological approaches to identify and characterize the taste bud cells that respond to salt and the peripheral ganglion neurons that convey sensory information from the taste buds to the brain. Scientists are using molecular analysis of taste and ganglion cells to identify the receptors, neurotransmitters, ion channels, and other key molecules that are involved in the perception of salt. These molecules can then be targeted as candidates for the development of taste modifiers (e.g., salt enhancers and substitutes). NIDCD-supported scientists are also mapping genes responsible for conferring salt taste preferences in order to better understand how genes influence food selection.

Existing evidence suggests that lowering the consumption of salt decreases sensory preference for salt. A recent study by NIDCD-supported scientists demonstrated a relationship between early dietary experience and salt preference, raising the possibility that a reduction of salt intake during infancy may reduce desire for high salt foods later in life. Several NIDCD-supported scientists are studying how dietary salt experience influences gustatory (taste) development and the neural organization of the taste areas in the brain. An understanding of how gustatory information is represented in the brain and how this representation is shaped by experience may help us develop strategies for reducing salt intake and improving overall health.

Item

Synapses. - The Committee supports research on genetic and cellular mechanisms of normal synapse function and on approaches to prevent or reverse deafness-caused disruptions. (p. 94)

Action taken or to be taken

Specialized junction sites, called synapses, enable nerves to communicate with each other by relaying signals from nerve to nerve. 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 changes both the neural circuitry of the auditory system and the properties of synaptic transmission. NIDCD funds numerous studies examining the genetic and cellular mechanisms of normal synaptic function and how brain connection patterns change (a phenomenon known as plasticity) as the cochlea processes sound. When attempting to restore hearing via cochlear implants or hearing aids, these changes must be considered. Knowledge of synaptic connectivity is critical for understanding the functional circuitry in different parts of the brain that are involved in hearing, such as the medulla, midbrain and the cortex.

NIDCD-supported scientists are examining normal synaptic transmission of hair cells of the inner ear, a highly specialized cell that acts as the primary sensory receptor of the auditory system. Current research projects focus on describing the physical organization of the synaptic junction, identifying the interactions of inner ear synaptic-complex proteins, and understanding the ion channels that regulate synaptic vesicle release from hair cells. In addition, NIDCD intramural scientists are also studying the molecular process that enables sound information to be processed so quickly and continuously (i.e., the speed of sound) to the brain. Using a structural and functional approach, the scientists learned how hair cell synapses synchronize multiple vesicle release. Through these studies, scientists are uncovering how synapses reorganize based on sensory experience, which can lead to the development of therapies for auditory learning.

NIDCD also supports research on disordered synaptic connections. NIDCD-funded scientists are using animal models to show that noise exposure previously believed to be at a non-damaging level does indeed compromise the integrity of the first auditory synapse. Knowledge regarding the long-term effects of noise on synapse function can be used to inform strategies that could minimize and prevent hearing loss, including the design of future therapies that may attenuate damage over the lifespan and increase an individual's ability to benefit from assistive hearing devices. 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 and overexposure to noise. NIDCD-supported scientists have also discovered that molecular receptors for the neuromodulator, serotonin, induce synaptic plasticity in the auditory cortex which appear initially disrupted by early-onset sensorineural hearing loss. This suggests that pharmacologic approaches may be developed to promote recovery of synapse transmission once hearing is restored by other means, such as by cochlear implantation.

Item

Tinnitus. - The Committee urges NIDCD to investigate preventions, treatments, and cures for tinnitus, which remains the most prevalent service-connected disorder for U.S. military personnel. Continuing research on the specific neural dysfunction responsible for tinnitus and on ways to suppress hearing system hyperactivity is essential. The Committee urges additional studies of the effect on tinnitus of stimulation of the vagus nerve with an implantable electrode.
(p. 94)

Action taken or to be taken

Tinnitus is characterized as the sensation of sound when it is not physically present. This disorder is caused by exposure to loud noise or damage to the cochlea, is commonly preceded by hearing loss, and has been linked to depression. The American Tinnitus Association estimates that 50 million Americans have experienced tinnitus, 16 million have sought medical attention, and two million are debilitated by the disorder. The U.S. Department of Veterans Affairs annual benefits report for 2011 lists tinnitus as the most prevalent service-connected disability for Veteran compensation.

Research on the specific changes in brain pathways that lead to tinnitus remains a priority for NIDCD. Noise-induced hearing loss (NIHL) appears to be the dominant factor associated with prolonged tinnitus, and recent studies indicate direct associations between the degree of hearing loss and tinnitus. Damage to the cochlea and auditory nerve appears to induce changes in higher brain centers, which then results in the onset of tinnitus. NIDCD supports basic research studies of tinnitus in animals with NIHL and supported a recent study in humans that demonstrated reduced activity in the auditory nerve, consistent with NIHL, but increased activity in higher brain centers. The translation of basic research findings into diagnostic tests for humans is essential for isolating specific neural changes that give rise to tinnitus and is the first step in developing an effective treatment.

One widely used approach for managing tinnitus is to mask it with background noise such as radio static. Recent results from an NIDCD-supported study demonstrated that continuous modulation of tone amplitude and frequency can make this approach more effective. Surprisingly, the use of “static” noise was determined to be the least effective approach to mask tinnitus. NIDCD is also funding research on the development of an integrated medicine approach for treatment of non-auditory emotional aspects of tinnitus, in addition to traditional sound-based masking therapy and education.

NIDCD continues to support research and development on electrical stimulation of the vagus nerve (a large nerve that runs from the head to the abdomen) to treat tinnitus. This approach has moved rapidly from tests of the concept in basic animal studies, through device development, to funding for a clinical trial. The project team is currently applying for an Investigational Device Exemption from FDA and hopes to begin the clinical trial by 2013.

National Institute of Mental Health (NIMH)

Senate Significant Items

Item

Autism. - The Committee commends NIMH for its leadership on autism research and encourages the Institute to ensure that such research focuses on both genetic and environmental causes. The Committee also encourages NIMH to collaborate with NIEHS regarding environmental causation. (p. 95)

Action taken or to be taken

The National Institute of Mental Health (NIMH) and the National Institute of Environmental Health Sciences (NIEHS) continue their commitment to identify and support innovative and high-impact biomedical research into the genetic and environmental causes of autism spectrum disorder (ASD). ASD research activities are coordinated across NIH through the NIH Autism Coordinating Committee (NIH ACC), which includes participation from seven Institutes and Centers (ICs).² The NIH ACC also closely follows the activities of the Federal Interagency Autism Coordinating Committee (IACC) and, in particular, works to ensure that research objectives - designated in the IACC Strategic Plan for Autism Spectrum Disorder Research-- are met as they apply to the missions of the NIH Institutes and Centers, including objectives targeting research on the possible genetic and environmental etiology of autism.³

ASD is a complex neurological disorder that affects children and adults with varying degrees of severity. To better understand the complexity of ASD, NIH supports research on the potential causes of the disorder, including inherited or spontaneous alterations in specific genes, exposures to environmental risks or hazards, or a combination of both genetic and environmental risk factors.

For example, a consortium of investigators supported by NIH identified spontaneous genetic mutations that were highly associated with the risk for transmitting ASD from parent to child. Moreover, fathers were four times more likely than mothers to transfer these specific genetic mutations to offspring, and the number of these genetic mutations was higher among older fathers.⁴ These spontaneous mutations may reflect cumulative environmental exposure as a father ages, reminding us that environmental factors may also contribute to autism.

NIH Institutes and Centers have also collaborated to support large research initiatives such as the Early Autism Risk Longitudinal Investigation (EARLI) study. Supported by NIEHS, NICHD, NIMH, and NINDS, the study examines risk factors in mothers of children with ASD at the start of a new pregnancy, documenting the development of the newborn siblings through age three.

² The 7 NIH ACC Institutes and Centers are: National Center for Complementary and Alternative Medicine (NCCAM), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Environmental Health Sciences, National Institute of Mental Health (NIMH), National Institute of Neurological Disorders and Stroke (NINDS), and National Institute of Nursing Research (NINR).

³ The IACC Strategic Plan may be accessed at: <http://iacc.hhs.gov/strategic-plan/2011/index.shtml>.

⁴ O’Roak BJ, Vives L, Girirajan S, et al. Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. *Nature*. April 5, 2012.

A second study, Markers of Autism Risk in Babies—Learning Early Signs (MARBLES), is an NIEHS-funded project investigating a number of environmental exposures that may contribute to ASD.

The Childhood Autism Risk from Genes and Environment (CHARGE) study is another ongoing study supported by NIEHS. Recent results from the CHARGE study suggest that maternal intake of folic acid from diet and supplements in the period before and after conception is associated with decreased risk for autism,⁵ while maternal metabolic conditions during pregnancy (e.g., diabetes, hypertension, obesity) increase risk.⁶

Item

Combination HIV Prevention. - With recent scientific advances demonstrating the promise of biomedical HIV prevention interventions, behavioral research is needed more than ever to bolster medication adherence and treatment uptake, document real-world decisionmaking processes associated with biomedical interventions, and better understand potential unintended and/or undesired consequences of biomedical interventions. The Committee urges NIMH to support a robust HIV/AIDS behavioral prevention research agenda that examines these factors and includes operations research to optimize combination HIV prevention. (p. 95)

Action taken or to be taken

The National Institute of Mental Health (NIMH) continues its commitment to support research to decrease the incidence of HIV/AIDS world-wide and decrease the burden of living with HIV/AIDS. As antiretroviral treatment (ART) strategies continue to improve, maintaining long term prevention and treatment efforts is critical, and requires combination strategies that include strong emphasis on behavioral self-management. Recent advances in HIV/AIDS prevention using ART as both pre-exposure prophylaxis (PrEP) for uninfected individuals, and continuous treatment of all infected individuals to decrease transmissibility (Treatment as Prevention, or TasP), have demonstrated that a combination of these and other biomedical approaches has the potential to make transformative changes in HIV/AIDS transmission. However, the variable results of different trial designs and target populations continue to illustrate that the gap to achieving consistent success is strongly behavioral. It is critical to develop better strategies to engage people to get tested and linked to care, but also to promote adherence to long term maintenance of treatment and care. NIMH continues efforts to integrate theoretically sound behavioral science into multiple biomedical approaches to significantly curtail the epidemic. Expanding collaborations across NIH Institutes and Centers, as well as other Federal agencies, is integral to the implementation of combination approaches in order to leverage resources and broaden the impact of this research.

To this end, NIMH is participating in a number of initiatives to foster targeted and collaborative research. NIMH recently issued funding opportunity announcements (FOAs) to stimulate research at the community level, and is co-sponsoring an FOA to support research

⁵ Schmidt RJ, Tancredi DJ, Ozonoff S, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (Childhood Autism Risks from Genetics and Environment) case-control study. *Am J Clin Nutr.* 2012 Jul; 96(1):80-9.

⁶ Krakowiak P, Walker CK, Bremer AA, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics.* 2012 May;129(5):e1121-8.

on HIV-associated conditions, treatment, and/or biobehavioral and social factors associated with HIV/AIDS in the context of aging.

In addition, NIMH is co-sponsoring the National Institute of Allergy and Infectious Diseases-supported AIDS Clinical Trials Networks, which create an infrastructure capable of performing combination HIV/AIDS research across multiple scientific disciplines and in collaboration with multiple Institutes, Agencies, and Organizations. Through these networks, NIMH is supporting several protocols that address the behavioral components of both PrEP and TasP, which are critical to successful implementation of these prevention strategies, such as acceptability, adherence, and long term maintenance.

Item

Mental Health Disparities. - Rural and minority individuals can be vulnerable to emotional disorders for a number of reasons. Greater rates of poverty among some ethnic and minority groups and rural populations, relationships between low socioeconomic status and some mental disorders, and greater risk of poverty among people with certain mental illnesses can create a vicious cycle. In addition, cultural differences in symptom expression and attitudes toward mental illness can make recognition and diagnosis of mental disorders in these populations difficult. Further, minorities living in rural areas are particularly likely to be medically underserved, facing significant barriers to getting needed mental healthcare. The Committee encourages NIMH to fund research efforts to find innovative ways to address mental health disparities in underserved populations, especially in designated Psychiatric Manpower Shortage Areas. (p. 96)

Action taken or to be taken

The National Institute of Mental Health (NIMH) continues to address behavioral and mental disorders among rural and minority individuals through research on risk, resilience, and access to mental healthcare, and by convening scientists to identify gaps and pertinent research questions. In 2012, NIMH issued a funding opportunity announcement, “Mechanisms Explaining Differences in Depressive and Anxiety Disorders across Racial/Ethnic Groups,” designed to stimulate research that helps to clarify cultural differences in symptom expression and the impact of socioeconomic status on mental illness. Additionally, three of NIMH’s largest ongoing studies include substantial numbers of participants from racial/ethnic minority groups and are expected to contribute significantly to the understanding of the relationship between socioeconomic status, cultural differences, and mental illness:

- The *Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS)*⁷ is the largest study of mental health risk and resilience ever conducted among military personnel. The findings from this potentially groundbreaking 5-year study will be applied to ongoing health promotion, risk reduction, and suicide prevention efforts in the Army and will inform efforts in the broader civilian population. Army STARRS is enrolling 100,000 participants, and minority participants will be enrolled in the same proportion as they are represented in the active duty Army. African Americans, for example, comprise approximately 20 percent of the Army.

⁷ More information on the Army STARRS project may be found at: <http://www.armystarrs.org/>.

- The *Recovery After an Initial Schizophrenia Episode (RAISE)*⁸ initiative seeks to change fundamentally the trajectory and prognosis of schizophrenia through coordinated and aggressive treatment in the earliest stages of illness. RAISE is designed to reduce the likelihood of long-term disability for people with schizophrenia. Implementation of the interventions that RAISE utilizes is further expected to reduce the financial impact of care on public systems. More than one-third of the study participants will be members of racial/ethnic minority groups. RAISE project sites also include rural communities and will consider strategies for reaching underserved populations.
- The *Neurodevelopmental Genomics Project* will examine risk and resilience factors for mental disorders in children. The impact of mental disorders frequently begins in childhood, and most lifelong, disabling disorders are apparent by age 14.⁹ The Neurodevelopmental Genomics Project will examine developmental trajectories and link observed behavior that suggests vulnerability to a disorder with brain structure and function and genomics data among a diverse group of children. Racial/ethnic minorities will make up more than 38 percent of this study population, ensuring that preventive and treatment interventions that arise from this study will be relevant to these communities.

In addition to NIMH's funded research initiatives in this area, the Institute's Outreach Partnership Program is another important means for delivering science-based information to communities across the country. This program disseminates NIMH research findings and educational materials to the public, including underserved populations, and also conducts targeted outreach activities to address mental health disparities that occur because of race, ethnicity, and geographic location, among other factors. State-based organizations competing to become NIMH Outreach Partners are now required to demonstrate that they will conduct programs to specifically reach historically underserved populations.

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 a result of treatable medical conditions such as cardiovascular, pulmonary, endocrine, and infectious diseases. The Committee urges NIMH to continue its collaborations with other Institutes, including NIDDK and NHLBI, to pursue research to better understand the causes and interventions needed to address this crisis. The Committee requests an update in the fiscal year 2014 congressional budget justification. (p. 96).

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 11 to 32 years earlier than the general population.^{10, 11} The National Institute of Mental Health (NIMH)

⁸ More information about RAISE may be found at: <http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml>.

⁹ Merikangas KR, He JP, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the 2001-2004 NHANES. *Pediatrics*. 2010, 125(1):75-81

¹⁰ Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Preventing Chronic Disease*. 2006 Apr; 3(2):A42.

¹¹ Druss BG, Zhao L, Von Esenwein S, et al. Understanding excess mortality in persons with mental illness: 17-year follow up of a nationally representative US survey. *Medical Care*. 2011; 49(6):599-604.

supports numerous studies, including co-sponsored research with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute (NHLBI), which aim to improve the general health of persons living with SMI and comorbid physical illnesses. These studies cover a broad range of treatable conditions associated with SMI that harm the health of these individuals (e.g., nicotine addiction, diabetes, obesity, cardiovascular disease) and contribute to their premature mortality.

The NIMH-supported Recovery After Initial Schizophrenia Episode Early Treatment Program (RAISE ETP) has enrolled 400 patients with early psychosis.¹² A primary goal of the RAISE-ETP intervention is to prevent participants from developing cardiovascular and metabolic abnormalities. This study will increase our understanding of how cardiovascular disease develops in people with schizophrenia and the impact of early detection and treatment.

NHLBI-sponsored research that explores the relationship between depression and cardiovascular disease outcomes include a small pilot study in patients with acute coronary syndromes and a randomized clinical trial in patients undergoing coronary artery bypass graft surgery; both studies showed that stepped-care approaches to treating depression yielded significant improvements in measures of depression and quality of life. The studies also identified some possible beneficial effects on cardiac outcomes. Major NIDDK-supported diabetes clinical trials, such as the Diabetes Prevention Program Outcomes Study and Action for Health in Diabetes, include measures of depression. NIDDK also encourages behavioral research as it relates to the impact of mental health on diabetes self-management.

NIMH and NIDDK co-sponsored the funding opportunity announcement (FOA) “Planning Grants for Translational Research to Improve Obesity and Diabetes Outcomes” to support research to improve obesity and diabetes care in people with SMI. NIMH and NHLBI, together with other NIH Institutes and Centers (IC), supported the FOA “Behavioral Interventions to Address Multiple Chronic Health Conditions in Primary Care”. This announcement will foster research on practical approaches for integrating and improving chronic disease management for primary care patients with multiple chronic conditions, including patients with SMI and other medical conditions.

In September 2012, NIMH convened the meeting “Research to Improve Health and Longevity of People with Severe Mental Illness,” in collaboration with NIDDK, NHLBI, and other NIH ICs. The goal of the meeting was to identify critical research gaps in improving the health and longevity of people with SMI and the most pressing research questions the ICs should consider addressing. Based on the discussions in that workshop, NIMH has proposed an initiative to support research to improve health and reduce premature mortality in people with serious mental illness. Additionally, in October 2012, NIDDK and NIMH jointly convened the International Conference on Diabetes and Depression, a multidisciplinary conference on the biology of co-occurring diabetes and depression, and on improved prevention and treatment approaches.

¹² More information about RAISE may be found at: <http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml>.

Item

Psychotropic Drugs and Children. - In a November 2011 letter to State Medicaid directors, HHS officials noted that children in foster care are prescribed antipsychotic medications at nearly nine times the rate of other children receiving Medicaid. A December 2011 study by GAO reported similar findings, noting that prescriptions to foster children in the States GAO analyzed were more likely to have indicators of potential health risks. The Committee is pleased that NICHD, in collaboration with NIMH, is working to better understand the impact of medications on the growth and development of children. In light of the clinical vulnerability of many children in foster care, the Committee encourages both Institutes to assign this research a high priority as well as to examine evidence-based, nonpharmaceutical interventions to treat children with behavioral and mental health issues. (p. 96)

Action taken or to be taken

Research on the effectiveness and safety of psychiatric medications in children continues to be an important priority at the National Institute of Mental Health (NIMH) and the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development (NICHD).

A recent study funded by NIMH, the National Institute on Drug Abuse, and the Agency for Healthcare Research and Quality examined national trends in the prescription of antipsychotic medications, comparing the years 1993-1998 to 2005-2009.¹³ The study found, among adults, that medical office visits including a prescription for an antipsychotic increased by 96 percent between these two time periods. Among youths (ages 20 and under), the increase was 570 percent. Another NIMH-funded study recently found within a Medicaid population that children in foster care remained on antipsychotic medications significantly longer than comparison children (an average of 222 days vs. 135), and were also more likely to be using two or more antipsychotics at the same time.¹⁴

NIMH continues to support studies on non-pharmacological, psychosocial interventions for children and is funding research to develop and test alternative treatments to medications for the management of depression, anxiety, and behavioral problems. Effectiveness trials are currently comparing different interventions for the treatment of children and adolescents with anxiety, major depression, and autism spectrum disorders.

As the lead NIH institute charged with implementing the Best Pharmaceuticals for Children Act, NICHD supports research on the use and usefulness of medications in children for behavioral and mental disorders, including an ongoing lithium trial for children with bipolar disorder. NICHD recently signed an inter-agency agreement (IAA) with the Health Resources and Services Administration to co-fund the Pediatric Research in the Office Setting (PROS) Network, specifically the sites using electronic health records. The IAA will enable researchers to access de-identified data on psychotropic medication use and related adverse events of these medications on children in pediatric primary care, including those living in foster care.

¹³ Olfson M, Blanco C, Liu SM, et al. National Trends in the Office-Based Treatment of Children, Adolescents, and Adults With Antipsychotics. *Arch Gen Psychiatry*. 2012 Aug; 6:1-10.

¹⁴ Dos Reis S, Yoon Y, Rubin DM, et al. Antipsychotic treatment among youth in foster care. *Pediatrics*. 2011;128:1459-1466.

Additionally, NIMH and NICHD are collaborating with other Federal agencies, such as the Administration for Children and Families (ACF) and the Centers for Medicare and Medicaid Services, in order to foster the implementation of evidence-based practices for child mental health treatment in the community. NIMH and NICHD partnered with the ACF and other Federal agencies in August 2012 to convene the conference “Because Mind Matters: Collaborating to Strengthen Management of Psychotropic Medications for Children and Youth in Foster Care.” The goal of this conference was to discuss ways of improving the current approach to mental health treatment for children in foster care.

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National Institute on Drug Abuse (NIDA)

Senate Significant Items

Item

Collaboration With the FDA. - The Committee applauds the role NIDA is playing to facilitate the growth of regulatory science at FDA's Center for Tobacco Products. The research NIDA oversees will inform policies on regulating tobacco-product advertising, labeling, marketing, constituents, ingredients, and additives. As such, the Committee commends NIDA for helping establish a science base for informing regulatory policies that are expected to influence tobacco-product risk perceptions, exposures, and use patterns in the short term, and to reduce tobacco-related morbidity and mortality in the long term. In particular, the Committee recognizes that large-scale research on national, longitudinal cohorts like the Population Assessment of Tobacco and Health study will be critical for assessing the impact of FDA regulatory authority over tobacco products and help to inform future activities. (p. 94-95)

Action taken or to be taken

Smoking is the single, largest preventable cause of disease, disability and death in the United States. Each year, more than 440,000 people die from smoking-related illnesses (nearly 1 in 5 deaths), mainly from cancer, heart, vascular and lung diseases, and another 8.6 million live with serious illness caused by smoking. Despite the risks, almost 35 million Americans report being daily smokers and approximately 6,500 Americans, most of them under the age of 18, start smoking each day.

In response, NIDA and NCI support a comprehensive research portfolio to elucidate nicotine's effects on the brain and body, devise effective prevention strategies (targeting young people in particular), and develop behavioral interventions and medications to help smokers quit for good. Effective tobacco control efforts are also critical for reducing tobacco use and related morbidity and mortality. NCI, for example, supports research to evaluate the effects of counter-marketing strategies, warning labels, and tobacco product packaging on tobacco use behavior, especially among youth.

Collectively, NIDA, NCI, and other NIH Institutes and Centers are collaborating with the FDA to further develop this science base to inform the policies and treatments needed to reduce tobacco use and attendant disease. For example, the Population Assessment of Tobacco and Health (PATH) study, the first large-scale NIH-FDA collaboration on tobacco regulatory science research since Congress granted FDA the authority to regulate tobacco products under the Family Smoking Protection and Tobacco Control Act (FSPTCA), is a national, longitudinal cohort study that will follow an estimated 59,000 adults and youth (12 to 18 years old) to assess susceptibility to tobacco use, patterns of use, risk perceptions, and resultant health impacts. The sample will include both males and females and persons of diverse racial, ethnic, and cultural backgrounds. Data collection will begin in fall 2013, with plans for four or more annual data collection waves. Outcomes will inform current and future regulatory options for the FDA to protect public health, including setting tobacco product standards and communicating the risks of tobacco use to the general public.

Other beneficial NIH-FDA collaborations on tobacco include: (1) the co-funding of additional NCI and NIDA projects to evaluate nicotine yield and delivery across different tobacco products, and (2) multiple funding opportunity announcements to encourage transdisciplinary research to guide FDA's regulation of tobacco product manufacture, distribution, and marketing. Research funded through these initiatives will investigate methods to assess toxicity, addictiveness and use of current, new and emerging tobacco products, and the impact of marketing and FDA regulatory action on future use, morbidity, and mortality. Finally, interagency partnerships such, as the NIH-FDA Joint Leadership Council and Tobacco Regulatory Science Partnership, will help sustain future cross-agency efforts relevant to tobacco regulation.

Item

Education. - The Committee recognizes and encourages the educational efforts of NIDA to inform the public of the deleterious effects of abused substances and the life-threatening dangers of drug addiction. Adolescents and returning veterans and their families are at a high risk for drug abuse and therefore should be areas of focus. (p. 95)

Action taken or to be taken

Because addiction typically starts in adolescence or even childhood, it is known as a developmental disease—one that can last a lifetime if untreated. That is why teens are a key audience for NIDA's health education efforts to raise awareness about the harmful health effects of substance use. NIDA continues its active outreach to young people and other vulnerable groups with information that can help them make healthy decisions. Examples include:

- *National Drug Facts Week (NDFW).* In its third year, NDFW is a health observance week designed to provide teens with scientific information to shatter common myths about drugs. Specifically, NDFW fosters community partnerships among scientific experts, teens, and Federal and private-sector organizations, and provides them with web-based materials to design and host local events. In November 2011, about 165 events were held in 47 states, and more than 166,000 teens received NIDA's teen booklet *Drugs: Shatter the Myths. During a live Drug Facts Chat Day, now in its 6th year, NIDA scientists answered nearly 1,700 questions from teens around the country.* The next NDFW observance is in January 2013. *NIDA for Teens Website.* NIDA's teen website provides a variety of ways for teens to learn about drug abuse and to engage with interactive quizzes, games, a blog, free downloads, and other offerings. Recently, NIDA added *PEERx* (<http://www.teens.drugabuse.gov/peerx/>), a website that contains information about prescription drug abuse and encourages teens to interact with the storylines presented and to share what they learn with peers. The Sara Bellum Blog *continues* to be highly successful, as demonstrated by the number of comments received and responded to from its mainly teen audience. The interactivity of NIDA's teen website *underlies* its success, with visits exceeding 133,000 each month.
- *Easy-To-Read Website.* NIDA's new Easy-to-Read website (<http://easyread.drugabuse.gov/>), designed for low-literacy adults, shares information about drug abuse science, prevention, and treatment. The website, which receives approximately 25,000 views a month, was developed with input from literacy educators, health care providers, faith and community groups, and others. In 2012, the Easy-to-Read website received a 2012 ClearMark Award of

Distinction and a Merit Award from the Web Health Awards: Honoring the Best Digital Health Resources.

- *Educating Health Care Providers.* Physicians are uniquely positioned to educate their patients about the harms of drug abuse. Therefore, NIDA is helping to educate medical students, residents, and practicing physicians about drug abuse, including prescription drug abuse (see *Prescription Drug Abuse pg 156*), so they in turn can educate the public.

Veterans are another vulnerable group (see *Military Personnel, Veterans, and Their Families pg 154*) to whom NIH targets outreach efforts. For example, an NCI grant is studying tobacco messages directed at the veteran community to inform the development of an educational outreach intervention to reduce tobacco use in the military.

Item

Medications Development. - The Committee encourages NIDA to continue its efforts to develop medications to treat diseases of addiction. (p. 95)

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 use 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 NIDA is using all available mechanisms to advance the development of addiction medications.

To garner more pharmaceutical involvement, NIDA is taking the approach of “de-risking” compounds in the early stages of discovery—awarding large grants up-front for shorter durations to encourage quicker results among closely monitored grantees, or to allow a change in direction as needed. This more nimble strategic approach was prompted in part by the successful clinical trial of Probuphine, supported by 2-year American Recovery and Reinvestment Act (ARRA) funding whose goals included increasing economic efficiency by spurring technological advances in science and health. Probuphine is a buprenorphine medication implanted under the skin that allows continuous medication delivery for 6 months after a single treatment. Titan Pharmaceuticals announced in October 2012 that it filed a New Drug Application (NDA) with the FDA. In 2012, NIDA awarded two grants using this mechanism to test the safety and efficacy of novel medications for cannabis and cocaine addiction.

Progress is also being made in developing anti-addiction vaccines, which work by inducing drug-specific antibodies that can prevent a drug from entering the brain. Although the NIDA-supported nicotine vaccine, NicVAX, did not meet its desired endpoints in Phase III testing—the clinical trial phase where large groups of people receive the medication to confirm its effectiveness and safety—it did achieve proof-of-concept showing that individuals with high levels of anti-nicotine antibodies had higher smoking cessation and abstinence rates. This finding has spurred research to improve vaccine potency by stimulating a higher immune response. To that end, NIDA-funded researchers have developed a novel way to evoke high-titer anti-cocaine antibodies in animals sufficient to inhibit cocaine’s reinforcing effects in the brain.

Recent studies highlight other NIDA strategies that include repurposing existing medications and using combination approaches for drug addiction. For example, the antioxidant N-acetylcysteine (NAC), a naturally occurring amino acid widely available as an over-the-counter supplement, reduced cocaine-seeking in both animals and humans. NAC also yielded positive results in reducing cannabis use in addicted adolescents ages 15 to 21, a vulnerable group for whom existing treatments show little efficacy. Finally, a new study shows that amphetamine salts plus topiramate work better for achieving abstinence from cocaine dependence than placebo.

NIDA is working to overcome the barriers that remain to developing anti-addiction medications. For example, NIDA is soliciting studies to identify health outcomes associated with changes in drug use. The identification of these health outcomes could provide regulatory authorities with alternative outcome measures besides abstinence, currently the only accepted outcome for demonstrating efficacy of an addiction medication. Another major barrier is the lack of medication compliance in clinical trials, critical to determining a medication's efficacy; thus NIDA is supporting studies to improve patient adherence. Other high-priority areas include preclinical evaluation of medications, identification of new molecular entities to treat substance use disorders, and research to advance innovative genetics screening technologies to enable targeted interventions.

Item

Military Personnel, Veterans, and Their Families. - The Committee commends NIDA for its 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. The Committee encourages NIDA to continue work in this area. (p. 95)

Action taken or to be taken

Many returning military personnel need help confronting a variety of war-related problems, such as traumatic brain injury (TBI), post traumatic stress disorder (PTSD), depression, anxiety, sleep disturbances, substance abuse (including tobacco, alcohol, and other drugs), suicidal thinking and suicide attempts, and breakdowns in family relationships. Often, these problems are interconnected, contribute to individual health and family relationship crises, and pose a great risk to the health of active, reserve, and guard military personnel, recently separated veterans, and their families.

As part of coordinative efforts noted by the committee, NIDA, together with NIAAA, NCI, 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 has resulted in multiple studies that are helping to fill gaps in understanding these problems. Projects include studies of how TBI influences drinking behaviors and related clinical care and policy, and how evidence-based web-intervention models for improving parenting practices and child adjustments in highly stressed civilian families could be adapted to meet military families'

needs. Other grantees are examining how to mitigate the risks of PTSD and substance use disorders (which often co-occur) following combat exposure, and how to enhance civilian engagement in developing and implementing effective military tobacco control policies. To further elucidate the issues involved, NIDA and NIAAA released two FY 2013 funding announcements with the DoD, Office of the Assistant Secretary of Defense/Health Affairs, and NCCAM to accelerate research on interventions that (a) reduce the onset and progression of alcohol, tobacco, and other drug use and abuse (including illicit and prescription drugs) and associated mental and physical health problems and (b) promote health-enhancing behaviors among active duty or recently separated (e.g., Iraq and Afghanistan) military troops, veterans, and their families.

Other recent NIDA activities focused on the military and their families include several outreach efforts aimed at creating or furthering productive collaborations with the military to raise awareness and share scientific findings about effective substance abuse prevention and treatment strategies. In 2012, NIDA staff conducted multiple symposia and panels at scientific meetings and served as expert consultants on substance abuse and related concerns for various Department of Defense initiatives geared to help returning veterans and their families with drug abuse, psychological resilience, family functioning, etc. (e.g., the Military Operational Medicine Research Program). NIDA staff have also been involved for the past 5 years in planning the Annual Trauma Spectrum Conference for researchers, practitioners, and families, and presented on a Federal panel at last year's conference in December 2012. The December 2011 conference focusing on prevention, diagnosis, treatment, and recovery for the Iraq and Afghanistan cohort was jointly hosted by NIH, VA, and DoD/Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury. Sessions revealed research findings for multiple related health conditions, including neuroimaging, substance use and co-occurring disorders, women's health, PTSD and depression, and implementation science.

Item

Prescription Drug Abuse. - Prescription drug abuse has been the focus of much work by NIDA and remains a high priority. The Committee encourages NIDA to maintain its comprehensive leadership role in the effort to halt this epidemic. (p. 95)

Action taken or to be taken

While most illicit drugs, cigarette smoking, and alcohol abuse have shown considerable declines over the past decade or so among teens, the abuse of prescription drugs has not. While the 2012 Monitoring the Future Survey (MTF) showed a drop in past-year nonmedical use of Vicodin among all grades, rates remain high, with 7.5% or 1 in 13 high school seniors reporting abuse of the medication. In addition, a recent NIDA-supported study among high school seniors found that 7 out of 10 past-year nonmedical users of prescription opioids also took at least one other drug, mainly marijuana (58.5%) and alcohol (52.1%). Abuse of these medications, particularly with alcohol, can lead to catastrophic consequences as evidenced by the quadrupling in unintentional overdose deaths from prescription opioid pain relievers from 1999 to 2009.

Prescription stimulant abuse is also a cause for concern. In the past several years, the percent of 12th graders reporting the nonmedical use of Adderall has increased from 5.4% in 2009 to 7.6%

in 2012. Stimulant-related emergency room visits also have increased markedly; from 2004–2010, visits nearly doubled to ~4,000 for ages 12 to 17 and more than tripled to ~9,400 visits for ages 18 to 24. Moreover, in 2012 nearly 6% fewer high school seniors reported that trying Adderall occasionally was harmful—an indication that use may continue to rise.

NIDA supports a diverse prescription drug abuse research portfolio that includes epidemiological studies of the patterns, trends, and motivations underlying prescription drug abuse; research to elucidate the factors that predispose someone to become addicted to prescription pain relievers and what can be done to prevent and treat it; and studies on the impact of prescription drug monitoring programs. NIDA also supports research on alternative pain relievers (new molecules, delivery systems, or combinations) that are less rewarding and less likely to produce addiction.

In addition, to raise public awareness about the magnitude of this problem and steps the public can take to address it, NIDA is working with the Office of the Surgeon General and other Federal agencies to release a *Surgeon General's Call to Action To Prevent Prescription Drug Abuse among Youth*. It addresses youth motivations for abuse, environmental influences in the culture at large, and other factors, such as drug sharing by friends and family members, which may contribute to this epidemic. The Call to Action outlines strategies for developing and implementing prevention programs (delivered via schools and community coalitions), creating national and local media campaigns, and improving clinician education and use of Prescription Drug Monitoring Programs to help prevent drug seeking from multiple doctors and drug sharing.

Prevention, education, and outreach are critical in curbing prescription drug abuse. For example, the **NIDAMED** initiative—NIDA's outreach to provide tools and other resources to medical and health professionals—encourages physician screening of tobacco, alcohol, and illicit and prescription drug abuse. NIDA has also taken the lead at NIH in supporting Centers of Excellence in Pain Education (CoEPEs) with a focus on minimizing risks of addiction and diversion. In May 2012, 12 CoEPEs were awarded to develop pain management curriculum resources for medical, dental, nursing, and pharmacy schools to advance the safe treatment of pain. In October 2012, the Office of National Drug Control Policy and NIDA launched two online continuing medical education courses—one focused on safe prescribing for pain, the other on managing patients who abuse prescription opioids—in partnership with Medscape. NIDA also has a new initiative known as PEERx (see *Education pg 151*), a website that encourages teens to interact with storylines about prescription drug abuse and to share what they learn with peers.

Item

Translational Research. - The Committee encourages NIDA to continue its efforts to understand how genetics, age, environment, and other factors affect the use of experimental drugs and the development of addiction. (p. 95)

Action taken or to be taken

The results of NIDA-supported research have helped debunk the notion that addiction reflects a character flaw, demonstrating instead that it is a disease of the brain. The scientific, social, and policy implications of this new understanding are profound as research continues to illuminate the multilevel factors that influence the risk of experimenting with a drug and becoming addicted

to it. Much of NIDA's multidisciplinary portfolio is devoted to the systematic identification and characterization of those factors and their interactions.

NIDA continues to support research on genetic/epigenetic variations that confer susceptibility to abuse and addiction—efforts that have enlarged our understanding of biological contributors. This has been particularly true in the area of nicotine addiction, where genetic studies have uncovered promising targets for new therapeutics while epigenetic studies have provided evidence that nicotine can prime the brain to make it more susceptible to cocaine's effects. Recognizing the untapped potential of “big data” and cross platform data mining, NIDA will continue to support and maintain comprehensive data repositories holding genetic information, imaging data, and clinical information to facilitate broader use of the data across disciplines and to enhance research capabilities through opportunities to combine data across studies.

Although NIDA supports research across all age groups, young people are an especially important target for our efforts, given the particular vulnerabilities inherent in the developing brain and the disproportionate influence that psychosocial processes taking place during childhood and adolescent development have on substance use and other risky behaviors. We now know that early temperamental dispositions (e.g., self-control), family experiences, and interactions with the larger environment influence whether adolescents will develop individual characteristics that will make them more or less vulnerable to using and becoming dependent on drugs. For example, a recent study of rural African American youths transitioning out of secondary school found that in carriers of a particular genetic variant affecting the actions of the neurotransmitter dopamine, high levels of life stress predicted cognitive vulnerability and increased drug use in adulthood. Accordingly, NIDA continues to invest heavily on research designed to understand the complex factors that make adolescence a period of such heightened sensitivity for addiction.

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National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Senate Significant Items

Item

Prevention and Brief Intervention. - The Committee applauds the release of NIAAA's new youth alcohol screening guide and encourages the Institute to continue to promote alcohol screening of children and adolescents. The Committee urges NIAAA to pursue its plans to evaluate the guide both for detecting risk of alcohol problems and as an initial screen for other risky behaviors. The Committee also commends NIAAA's efforts to develop a matrix of interventions for addressing alcohol problems on college and university campuses and in the surrounding communities. Providing information on the effectiveness, cost, personnel requirements, and ease of implementation of individual and environmental interventions will assist college and university presidents and other administrators as they work to reduce harmful alcohol use among their students. The Committee recognizes the critical role of psychological research in understanding and addressing underage drinking. (p. 94)

Action taken or to be taken

Data from NIAAA's *National Epidemiologic Survey on Alcohol and Related Conditions* (NESARC) indicate that people between the ages of 18 and 24 have the highest prevalence of alcohol dependence in the U.S. population—meaning that, for most, drinking started in adolescence. This data, coupled with that from other national surveys showing the popularity of binge drinking among adolescents, prompted NIAAA to produce a guide for screening children and adolescents for risk for alcohol use, alcohol consumption, and alcohol use disorders (AUDs). The new screening guide, *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*, developed by NIAAA in collaboration with a working group of experts, was made available in early fall 2011. The guide consists of an easy to use, age-specific, two-question screener for current and future alcohol use, as well as background information on underage drinking, and detailed supporting material on brief intervention, referral to treatment, and patient confidentiality. The screening process will enable health practitioners to provide information to patients and their parents about the effects of alcohol on the developing body and brain in addition to identifying those who need any level of intervention. In November 2011, NIAAA issued a Funding Opportunity Announcement to solicit applications to evaluate the new NIAAA alcohol screener for youth. Although the questions were empirically developed, are based on a vast amount of data from national surveys as well as numerous prospective studies, and have high sensitivity and specificity in the sample studied, it is important that the precision of the screener be evaluated in practice. Applications were sought that would evaluate the two question screener in youth ages 9 to 18 both: 1) as a predictor of alcohol risk, alcohol use, and alcohol problems including AUDs; and 2) as an initial screen for other behavioral health problems, for example other drug use, smoking, or conduct disorder. Five projects have been funded.

NIAAA also continues to provide leadership on college drinking prevention. For over a decade, NIAAA has invested substantial resources in addressing college drinking, supporting research on interventions at both the individual and environmental levels. In 2011, at the request of NIAAA's newly established College Presidents Working Group, NIAAA commissioned a team

of experts to develop a “matrix” of college interventions to help college administrators navigate the many available interventions when making decisions about what to implement on their respective campuses. For each individual- or environmental-level strategy included in the matrix, information is provided about the amount and quality of available research, estimated effectiveness, estimated cost, staffing needs, barriers related to implementation, and time to implement - all factors relevant to campus and community leaders as they evaluate their current approaches, and as they consider additional strategies. Simultaneously NIAAA is developing a computerized searchable tool and accompanying materials based on the matrix. The ultimate goal is to provide science-based information in accessible and practical ways to facilitate its use as a foundation for college drinking prevention and intervention activities.

Psychological research has informed both of these activities and continues to play a significant role in the development of intervention strategies. Recognizing that approaches informed by behavioral science research will be important as we address some of the nation’s most pressing public health problems including underage and college drinking, NIAAA’s Acting Director serves on the HHS Behavioral Health Coordinating Committee where he co-chairs the Subcommittee on Alcohol Policy and Underage Drinking.

National Institute on Minority Health and Health Disparities (NIMHD)

Senate Significant Items

Item

Diabetes. - The Committee recognizes that more research and education are needed on the disparate effects of diabetes on minority populations. The Committee urges NIMHD to expand its research on pre-diabetes and diabetes, particularly type 2 diabetes in minority populations. This research should identify clinical, socioeconomic, geographical, cultural, and organizational factors that contribute to diabetes in such populations. Specifically, the Committee encourages NIMHD to analyze behavior and obesity. (p. 97)

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 clinical, socioeconomic, geographical, cultural and organizational factors contributing to diabetes rates in racial and ethnic minorities. For example, a project funded at the State University of New York - Albany is studying whether socioeconomic status (SES) and known risk and protective factors are correlated with reductions in the risk for co-morbid depression and diabetes, with special attention to low income populations in a nationally representative sample of African Americans and Caribbean Blacks. Another project, funded through the NIMHD Community Based Participatory Research Initiative, examines the effectiveness of an integrated educational, behavioral, and psychosocial intervention to achieve a 10 percent reduction in mean glycosylated hemoglobin (HbA1c) among economically diverse African Americans who have physician-diagnosed type 2 diabetes. HbA1c measures the average level of blood glucose over the past 3 months and indicates how well diabetes is being controlled. Also, the biomedical research study, *Vitamin D Status, Cardiovascular Health and Diabetes in American Indians*, is studying how low vitamin D levels are related to the increased risk of cardiovascular disease and type 2 diabetes mellitus by impacting the function of the inner lining of blood vessels. It is hypothesized that vitamin D supplementation should lead to the improvement of cell function thus reducing cardiovascular disease and diabetes mellitus risk.

In recognition of the importance of diabetes, NIMHD has expanded its portfolio of diabetes research projects through its Centers of Excellence (COE) program. For example, a project funded under the NIMHD COE program entitled, *Intestinal FABP, Dietary Fat and Type 2 Diabetes in Mexican Americans*, examines the role of genetic differences that effect how individuals respond to the amount and type of fat in the diet. In particular, the project focuses on the interaction between dietary fat intake and different kinds of the intestinal fatty acid binding protein as a possible mechanism for the early onset and higher severity of type 2 diabetes mellitus in Mexican Americans. The project *Translating Lifestyle Intervention into the Community Clinic and Community* delivers a 12- month lifestyle intervention program that seeks to promote caloric restriction and increase moderate-intensity physical activity among minority and lower-income men and women with type 2 diabetes mellitus who are overweight or obese. The intervention is designed to achieve 7 percent weight loss. In addition, NIMHD funds health disparities research focused on diabetes through the investigator-initiated research grants

program using the R01 funding mechanism. For example, *Understanding Health Disparities in the Progression of Type 2 Diabetes*, examines the effect of traditional preventative care among pre- or borderline, early onset, and poorly-controlled type 2 diabetes patients and the inter-relationships among stress, health behaviors, and physical and mental health at these three distinct points of diabetes progression. New diabetes projects funded under this program include the project, *Weight Gain, Type 2 Diabetes and Factors that Affect Neuroendocrine Function*, which examines factors that may contribute to the epidemic of obesity and type 2 diabetes in African American women. This project examines whether higher exposure to psychosocial stressors, such as preterm delivery with a low birth weight, victimization, depression, and sleep deprivation, unfavorably alter the neuroendocrine system. The neuroendocrine system is made up of the nervous and hormonal systems, which both interact to control important body functions like growth and the regulation of weight. It is hypothesized that psychosocial stressors may impair the body's ability to regulate weight and therefore contribute to increased risk of weight gain and type 2 diabetes. The project *Disparities in Chronic Illness Care for Patients with Language Barriers* investigates the impact of language barriers on medication adherence and appropriate service utilization for diabetes mellitus, hypertension, and high cholesterol. Diabetes research continues to be a priority for NIMHD. Through its programs, the Institute will continue to support diabetes research and encourage applications with an emphasis on diabetes.

Item

Obesity. - The Strategic Plan for NIH Obesity Research emphasizes the need for a transdisciplinary, multifaceted approach to address the complex factors that have resulted in the growing obesity problem in the United States. The Committee supports NIH's actions to date and the findings of the task force, but remains concerned that while the essential plan and direction may be in place, a better mechanism is needed to coordinate a trans-NIH, multidisciplinary effort to address the complicated nature of the obesity problem. The Committee urges NIH to intensify its investment in obesity research, in particular in populations that are most affected—racial and ethnic minorities, low-income populations, and rural populations. The Committee again strongly recommends that NIH review the benefits of establishing a Comprehensive Center of Excellence for Obesity Research and Prevention within NIMHD to better coordinate efforts within NIH and with other Federal agencies. The Committee believes that a comprehensive center could serve to capitalize on the health disparities efforts already under way at NIMHD and leverage both intramural and extramural research programs across NIH. (p. 97)

Action taken or to be taken

The NIH Obesity Research Task Force, of which NIMHD is an active member, 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 and continues to meet to explore research approaches that will foster collaboration across NIH Institutes and Centers focusing on molecular, genetic, behavioral and environmental factors. NIH supports many studies that include disproportionately affected racial and ethnic groups and socioeconomically disadvantaged populations.

Every five years, NIMHD is required to codify a NIH-wide strategic plan for minority health and health disparities research. The FY 2014-2018 NIH Health Disparities Strategic Plan and Budget is currently under development by the NIMHD in consultation with the other NIH Institutes and Centers. In light of these efforts, NIMHD will undertake a review of the benefits of establishing a Center of Excellence for Obesity Research and Prevention within NIMHD to better coordinate efforts within NIH and with other Federal agencies.

Regarding other trans-NIH activities, NIMHD is collaborating with the National Center for Advancing Translational Sciences (NCATS) to support a new Clinical and Translational Science Award (CTSA), the Miami Clinical and Translational Science Institute (CTSI). The Miami CTSI will use a transdisciplinary, community-partnered approach to achieve the orchestration of research programs, services, resources and training to improve population health and reduce health disparities in South Florida. Obesity is one of four priority areas.

NIMHD continues to foster transdisciplinary research on obesity through its own programs as well. Funded projects fall within three thematic areas: (1) biological/genetic determinants of obesity, (2) social/environmental determinants of obesity, and (3) lifestyle interventions to prevent or reduce obesity.

Biological/Genetic Determinants of Obesity: Active projects examine genetic or biological factors that impact the susceptibility, severity, or course of obesity in health disparity populations. For example, the Dillard University Center of Excellence (COE) is examining the role of pro- and anti-inflammatory markers that underlie the relationship between obesity and asthma, as well as the impact of weight loss on inflammatory pathways in obese African American adolescents. The COE at Jackson State University, in collaboration with the University of Alabama and Historically Black Colleges and Universities in Mississippi, will study how genetic factors interact with social and environmental determinants of obesity health inequities.

Social/Environmental Determinants of Obesity: Active projects examine the complex interplay between social, cultural, environmental, psychological, and biological factors that drive disparities in obesity. The University of Michigan COE is studying the large disparities in obesity and type 2 diabetes among Latinos as a reflection of the joint effect of intergenerational transmission of socioeconomic factors, cultural characteristics, behaviors, biology, and other risk factors accumulating over the life course. The New York University School of Medicine COE is using a faith-based and community-based participatory research approach to elucidate the clinical, behavioral, social and cultural mechanisms that link acculturation, stress, and obesity in South Asian populations in New York City.

Lifestyle Interventions to Prevent or Reduce Obesity: Active projects develop community-based, culturally-grounded interventions to address modifiable social and behavioral risk factors to combat obesity. The University of North Texas COE will use a community-based participatory research (CBPR) approach to conduct a randomized clinical trial for reducing obesity among African- American women in church settings. The Wake Forest University COE will conduct a randomized controlled trial of a culturally adapted, church-based lifestyle intervention to reduce weight and diabetes risk in obese Latinos. In addition, the NIMHD CBPR Initiative has

supported a number of community-developed lifestyle intervention projects to improve fitness, nutrition, and obesity and diabetes risk in children and adults in a variety of health disparity communities.

National Center for Complementary and Alternative Medicine (NCCAM)

Senate Significant Items

Item

Access to Natural Product Collections. - The Committee continues to applaud NCCAM's efforts to increase access to comprehensive and professionally organized natural product libraries, which are a major source of pharmaceutical leads and therapeutic agents. (p. 97)

Action taken or to be taken

Advancing research on natural products is identified as a priority area in NCCAM's Strategic Plan. Natural product screening is one important element in implementing the plan. NCCAM is currently 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.

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National Center for Advancing Translational Sciences (NCATS)

Senate Significant Items

Item

Clinical and Translational Science Awards [CTSAs]. - The Committee encourages NCATS to continue the focus of the CTSA program on the full spectrum of translational research. (p. 98)

Action taken or to be taken

The CTSA program supports a national consortium of medical research institutions that are transforming the way biomedical research is conducted. Its goals are to accelerate the translation of laboratory discoveries into treatments for patients, to engage communities in clinical research efforts, and to train a new generation of clinical and translational researchers.

The program seeks to strengthen the full spectrum of translational research. Institutional CTSA awards are the centerpiece of the program, providing academic homes for translational sciences and supporting research resources necessary for local and national research communities to improve the quality and efficiency of all phases of translational research. The importance of support for the full spectrum of translational research is emphasized in the July 2012 solicitation for Institutional CTSA awards (<http://grants.nih.gov/grants/guide/rfa-files/RFA-TR-12-006.html>).

Item

Congenital Diaphragmatic Hernia [CDH]. - The Committee encourages ORDR to support dedicated research funding directed for CDH, which affects approximately 1,600 babies in the United States every year. The Committee urges ORDR to put a high priority on research related to finding the causes of CDH and requests an update in the fiscal year 2014 congressional budget justification. (p. 98)

Action taken or to be taken

CDH is a birth defect that presents as a hole in the diaphragm that becomes apparent at birth or shortly thereafter when an infant has difficulty breathing. The hernia (hole) facilitates organs from the abdomen moving into the chest, thereby creating the breathing difficulties. According to Boston Children's Hospital, CDHs affect approximately 1 in every 2,500 babies.

The Eunice Kennedy Shriver Institute of Child Health & Human Development (NICHD) and the National Heart, Lung, and Blood Institute (NHLBI) are the lead institutes in research in this area. NICHD supports research on a wide range of congenital defects and their causes in humans, including the basic biological processes underlying both normal development and their formation of anatomical and functional birth defects such as CDH. The institute also funds research on whether particular treatments and interventions, such as extracorporeal membrane oxygenation (ECMO), can be used in infants to overcome their severe respiratory problems. Recently, NICHD brought together a panel of experts to look at the state of the science on whether the timing of surgical repair can increase an infant's chances of survival. The conclusion of the

panel was that available evidence is still insufficient to make that determination. The Institute currently is planning more research to help answer this question.

NHLBI focuses on the pulmonary effects of this defect. Congenital diaphragmatic defects are relatively common birth defects with high morbidity and mortality caused primarily by underdevelopment of the lung air spaces (pulmonary hypoplasia) and pulmonary hypertension. NHLBI-supported investigators are seeking to identify and characterize novel genes associated with CDH. This information could yield clues about the genetic changes causing CDH in some children. Investigations of the molecular mechanisms underlying CDH have identified a mutation in a gene called *Fog2* that causes a diaphragmatic defect with pulmonary hypoplasia. This gene is the first to be implicated in CDH. Other genes related to the *Fog2* pathways are now being studied to better understand the causes of this often life-threatening condition. The role of pulmonary blood flow and pulmonary vessel maturation in CDH on lung development will also be studied.

The Office of Rare Disease Research (ORDR) does not support research in this area, but staff meets frequently with patient advocates to explore ways in which greater research interest could be accomplished. ORDR, with NICHD and NHLBI, will explore whether a larger scientific meeting could fill this need, given that NICHD recently brought together a panel of experts to discuss CDH.

Item

Dystonia. - The Committee commends ORDR's support of the Dystonia Coalition Patient Registry. (p. 98)

Action taken or to be taken

The Dystonia Coalition Patient Registry was made available to the public on December 1, 2011. As of August 28, 2012, 2,654 patients had registered. Patient advocacy groups are 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 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 on October 20-22, 2011, and introduced to European patient advocacy groups in attendance.

Item

Hereditary Angioedema [HAE]. - The Committee recognizes that few treatment options are available for HAE and that they are not effective for all patients. The Committee encourages ORDR to continue to reinvigorate HAE research at NIH and help identify new pathways for interventions. (p. 98)

Action taken or to be taken

Hereditary angioedema (HAE) is a rare genetic disorder. HAE patients suffer from swelling of the hands, feet, abdomen, face and /or throat. The latter, especially, is a major medical emergency that can be fatal. Estimates for the prevalence of HAE range from 1 in 10,000 to 1 in 50,000 people in the U.S.

The Clinical and Translational Science Awards (CTSA) at Mount Sinai Medical Center and the University of Colorado Health Sciences Center conducted a Phase III study titled, "Icatibant for Subcutaneous Injection in Patients with Acute Attacks of Hereditary Angioedema". The results of these studies were used to support an Investigational New Drug (IND) Application which led to FDA approval of Firazyr (icatibant) as a third treatment for HAE. The injection can be self-administered for acute attacks of HAE in people ages 16 years or older (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm269616.htm>).

ORDR staff met with representatives of the U.S. Hereditary Angioedema Association (HAEA) on January 30, 2012, and encouraged the association to develop, together with research investigators, a grant application for a scientific conference. The goals of the conference would be to identify new research opportunities and develop a research agenda containing research priorities for HAE to help all patients with this disease. Such a conference could create significant research interest in this rare disease in the United States. NCATS has not yet received an application from HAEA.

Item

Rehabilitation Research. - The Committee encourages NCATS to include rehabilitation research as a priority area of investigation. (p. 98)

Action taken or to be taken

The mission of NCATS is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. NCATS is actively participating on rehabilitation-related committees, initiatives, and events and by providing funding for innovative rehabilitation research.

The following are examples of rehabilitation-related activities in which NCATS is involved:

- Representation on the trans-NIH Rehabilitation Research Coordinating Committee. This committee recently participated in the community-requested NIH Blue Ribbon Panel on Rehabilitation Research, which convened improve coordination of research funding across NIH and to develop a trans-NIH strategic plan for rehabilitation research.
- Representation on government-wide activities related to rehabilitation technologies, such as President Obama's National Robotics Initiative, World Technology Evaluation Center (WTEC) Human-Robotics Interaction and mobility technologies meetings sponsored by the National Science Foundation, and the Assistive Technology/Technology Forum Subcommittee of the Interagency Committee for Disability Research.
- Participation in the National Naval Medical Center, Walter Reed Army Medical Center, and Dept. of Defense research and development events that focus on the topics of

mobility, reduction of fatigue, prostheses and orthotics, and virtual reality research, which can lead to improved function and mobility for military personnel and civilians with mobility challenges or limb loss.

- Participation in the trans-NIH Traumatic Brain Injury Research Network and planning for the Federal Interagency Conference in Traumatic Brain Injury.

The following are a few examples of projects in rehabilitation research supported by NCATS:

- The University of Florida Clinical and Translational Science Award (UFL CTSA) supports research in muscle perfusion and the ability of skeletal muscle to recover following injury. The UFL CTSA is also conducting research on walking control and recovery after spinal cord injury.
- In collaboration with NASA, NCATS supports the University of Texas Medical Branch, Institute for Translational Science Clinical Research Center in Galveston, TX to study the effects of bed rest and to develop physical activity interventions to reduce deconditioning.
- Innovative Design Labs, Inc., in Minnesota received a Small Business Innovation Research (SBIR) grant to create a clinically viable tool to enable diagnosis and treatment-tracking of low back pain patients using a new system for measuring spinal motion and linking that to functional motion.

NCATS will continue to support clinical innovation in the vast array of rehabilitation research and activities through federal research program development and competitive funding of innovative research.

Item

Therapeutics for Rare and Neglected Diseases [TRND] Program. - The Committee commends NIH for establishing and growing the TRND program, and encourages NIH to fund the projects with the highest likelihood of success, regardless of disease state. In particular, the Committee commends TRND for supporting a Fragile X partnership to accelerate potential new treatments that benefit patients with this rare and neglected disease. The Committee also encourages TRND to continue supporting development of treatments for Duchenne muscular dystrophy to bridge the gap between a basic research discovery and the testing of drugs in humans. (p. 99)

Action taken or to be taken

The goal of the National Center for Advancing Translational Sciences (NCATS) Therapeutics for Rare and Neglected Diseases (TRND) program is to encourage and speed the development of new treatments for rare and neglected diseases by stimulating research collaborations among NIH and academic scientists, nonprofit organizations, and pharmaceutical and biotechnology companies. TRND uses predefined review criteria to ensure that projects have the highest likelihood of success, which include determination of target and therapeutic mechanisms, strength of the data package, feasibility to reach First in Human clinical trials, medical impact relative to current Standard of Care, and likelihood of adoption into health care practice.

TRND has built a portfolio of 16 therapeutic development projects since its inception, aiming to bring novel treatments to rare and neglected disease patients. Among the 16 projects, two were

established to develop novel therapeutics for Duchenne muscular dystrophy (DMD), a disease that puts patients in wheelchairs before they reach 12 years of age. The candidate therapeutics will be tested for safety in a series of FDA mandated pre-clinical studies and, if the compounds are found safe, in clinical trials. For one of the DMD projects, an Investigational New Drug (IND) application to the FDA is planned to be filed in the 4th quarter of 2013, with the start of testing in human clinical trials planned for 2014. The second potential therapeutic molecule has been taken back by the TRND collaborator to continue its development in house.

Fragile X Syndrome (FXS) is the most common inherited cause of mental impairment and the most common known single-gene cause of autism. In 2011, TRND established a collaboration with a California-based small biotech company, Afraxis, to develop therapeutics directly targeting an FXS-related biological pathway. This project was deactivated from the TRND portfolio at the end of 2012 when Afraxis formed a new alliance to pursue other disease targets.

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National Library of Medicine (NLM)

Senate Significant Items

Item

Disaster Information Management. - The Committee applauds NLM's support of the Disaster Information Management Research Center [DIMRC], which has made important contributions to the Nation's disaster preparedness and response efforts through the rapid creation of information resources for specific events; development of innovative information tools to aid in disaster preparedness, response, and recovery; the establishment of a disaster information specialty among librarians; and its participation in the Bethesda Hospital Emergency Preparedness Partnership. The Committee encourages NLM to continue to work through DIMRC with Federal and non-Federal partners, including the library community, to identify and implement best practices for maintaining access to health information before, during, and after disasters; develop innovative resources and tools to aid emergency responders and managers; collect, organize, and disseminate disaster health information; promote the development of disaster information specialists; engage the library community in disaster information management; conduct research into disaster health informatics; and develop and export community-based models of health resiliency during disasters. (p. 99)

Action taken or to be taken

NLM's Disaster Information Management Research Center (DIMRC) continues to make significant progress in developing innovative tools, services, and expertise in disaster information management to assist with the Nation's disaster preparedness, response, and recovery efforts. DIMRC continues to enhance and expand its resources for emergency responders in managing hazardous materials (HazMat) and chemical, biological, radiological, and nuclear (CBRN) events, and has ported such resources to multiple new platforms including mobile devices (iPhone, iPad, iPod touch, Android, and Blackberry). NLM works with multiple agencies, including the HHS Assistant Secretary for Preparedness and Response (ASPR), the Centers for Disease Control and Prevention (CDC), the National Cancer Institute (NCI), the Department of Homeland Security (DHS), and the Department of Transportation (DOT), on these resources. With more than 400,000 downloads worldwide, these mobile apps and tools provide emergency responders and other disaster personnel with quick and easy access to tailored information regarding hazardous chemicals and biological and radiological agents. NLM also is currently collaborating with ASPR to design an interactive version of the All-Hazards Plan, which is used for managing the federal medical and public health response to disasters (as called for in Emergency Support Function 8 of the National Response Framework).

NLM is also involved in efforts to provide authoritative, appropriate, and timely information for busy emergency personnel that will help them avoid information overload when preparing for, responding to, and recovering from major incidents. NLM has worked with the Medical Library Association (MLA) to develop a new specialization in disaster information management for librarians and other information professionals so that they can assist the disaster workforce in collecting, organizing, and disseminating relevant information. Librarians are encouraged to earn an MLA certificate as a disaster information specialist by taking a series of courses to

enable them to understand the information needs of the disaster workforce, learn about relevant tools and resources, and identify methods for working in their communities. With the modification of the Stafford Act to include libraries as critical infrastructure following disasters, ensuring that library staff is ready to assist the disaster workforce and the general public is extremely important. From providing internet and computer access in a community to serving as members of hospital incident command teams, librarians are finding new and unique ways to assist in all phases of disaster management.

NLM continues to work with the Bethesda Hospitals' Emergency Preparedness Partnership (BHEPP) to assist the partner hospitals in managing medical surge in a large scale event. NLM developed an electronic patient tracking and management system that won an HHS Innovates award in 2012. This system includes a digital pen used when triaging patients, a radio frequency identification (RFID) system to tag patients and monitor their position within and between the partner hospitals, and a patient data exchange to seamlessly exchange patient information among partner hospitals. In addition, NLM designed and conducted the first Hospital Incident Command System exercise in a virtual world to test the feasibility of simulations to provide an enhanced training environment and opportunities for hospital staff.

NLM continues to develop and collect information resources on specific disaster topics and events to aid in situational awareness, response, and long-term recovery from disasters. NLM recently developed resources related to the 2012 drought and the 2011 earthquake, tsunami, and radiation incident in Japan. NLM continues to collect disaster health literature in PubMed and the Resource Guide for Disaster Medicine and Public Health to ensure access to authoritative, timely information.

Office of the Director (OD)

Senate Significant Items

Item

Alzheimer's Disease. - The long-term costs of Alzheimer's disease, both in terms of lives and resources, are enormous. The Committee strongly urges the Director and all relevant ICs to increase funding for research on Alzheimer's disease to the greatest extent possible within their budgets. However, the Committee strongly disagrees with the President's budget request to allocate \$80,000,000 of the PPH Fund for Alzheimer's disease research at NIH. NIH research is not an appropriate use of the PPH Fund. Additionally, the Committee believes it would set a dangerous precedent to provide specific amounts of NIH funding for individual diseases. The Committee notes that it took the same position in fiscal year 2010 when the administration proposed allocating specific levels of funding for cancer and autism research. The Committee also notes that NIH has flexibility to prioritize funding for individual diseases when the scientific opportunities and the number of high-quality applications warrant an increase. HHS took this very approach in April when it announced a transfer of \$18,300,000 of fiscal year 2012 funds within NIH, as part of an overall strategy to increase NIH's investment in Alzheimer's research by \$50,000,000. The Committee recommends that NIH allocate resources for Alzheimer's research according to the priority research recommendations included in the National Alzheimer's Plan required under the National Alzheimer's Project Act. NIH is also encouraged to consider entering into public-private partnerships to accelerate the discovery and development of small molecule therapeutics that could potentially improve the symptoms and modify the course of Alzheimer's disease. (p. 100)

Action taken or to be taken

NIH is committed to addressing, through the thoughtful allocation of available resources, the research goals set forth in the National Plan to Address Alzheimer's Disease (AD), as well as the recommendations provided by experts at the Alzheimer's Disease Research Summit 2012, both of which will facilitate our achievement of the milestones established in the National Alzheimer's Project Act (NAPA). In doing so, we will be mindful of the necessity of balancing the scientific opportunities of the Alzheimer's research community with the agency's many other compelling priorities. To this end, we anticipate revisiting our plans and priorities on at least an annual basis, with continued regular consultation with public and private sector advisors.

In response to the Summit recommendations, NIH released four solicitations for research grant applications in early FY 2013, including initiatives supporting identification of therapeutic targets, drug development, and clinical trials of preventive and therapeutic interventions. The initial response from the research community has been enthusiastic, and we anticipate funding highly meritorious applications based on availability of funds.

The benefit of innovative public-private partnerships to accelerate the discovery and development of effective treatments for AD was a major topic of discussion at the AD Research Summit. A relevant ongoing initiative is the NIH Blueprint Neurotherapeutics Network, which was established to bridge the gap in drug development between academic and industry research.

Network investigators working with small molecule compounds can gain access to a robust “virtual pharma” network to discover neurotherapeutic drugs, receiving both funding and no-cost access to contracted drug discovery services that are not typically available to the academic research community, including medicinal chemistry optimization, Investigational New Drug (IND)-directed pharmacology and toxicology, and Phase I clinical testing. Two Network projects focused on AD therapeutics are currently active, and we anticipate that more will be initiated in the near future.

In addition, the NIA’s AD Translational Program, composed of several funding initiatives, continues to support the discovery and preclinical development of novel candidate therapeutics for age-related cognitive decline, mild cognitive impairment, and AD. Over 40 novel compounds are currently in preclinical development as part of this effort, and several of these compounds have been picked up by industry partners for full-scale clinical testing.

Finally, genome-wide association studies and other emerging high-throughput technologies have generated thousands of new drug targets for a number of diseases and conditions. NIH and pharmaceutical industry representatives are establishing a new consortium to identify the most promising candidate drug targets for further development. The group’s initial focus will be upon Alzheimer’s disease, schizophrenia, type 2 diabetes, and immune-mediated diseases, and we anticipate that consortium activities will be under way by early 2013. In addition, NIA will sponsor a meeting in February to discuss the potential development of a public-private partnership to share preclinical data, drug targets, and animal models in a precompetitive space to facilitate new therapies for AD. We will pursue other opportunities for public-private partnerships as appropriate.

Item

Career Development Awards for Clinical Researchers. - The Committee is encouraged by the Director’s efforts to strengthen the biomedical research workforce and recommends the continued awarding of NIH Career Development Awards, or “K” Awards, to train clinical researchers. (p. 100)

Action taken or to be taken

NIH maintains that clinical researchers are essential contributors to the advancement of biomedical research, and remains committed to maintaining the career development activities (K awards) that allow clinicians to acquire and enhance their research skills and to become independent investigators.

Much of NIH’s career development support for patient-oriented clinical investigators has been concentrated in three activities; the Mentored Patient-Oriented Research Career Development Award (K23), Midcareer Investigator Award in Patient-Oriented Research (K24), and the institutional career development awards associated with the Clinical and Translational Science Awards program (CTSA). In FY 2012, NIH made a total of 997 new and continuing K23 awards, 242 K24 awards, and provided career development support to more than 500 individuals at just over 60 CTSA sites.

In their efforts to reduce the time it takes for laboratory discoveries to become treatments for patients, CTSA sites around the country provide a particularly rich environment for promoting multidisciplinary approaches to clinical studies and are an excellent setting for developing the careers of patient-oriented researchers.

A 2011 evaluation of NIH's individual mentored career development award (http://grants.nih.gov/training/K_Awards_Evaluation_FinalReport_20110901.pdf) found that K23 awardees obtain NIH research grant support and publish research findings at significantly higher rates than individuals with similar research backgrounds who did not receive these awards. The success of these career awardees provides compelling reasons for NIH to continue supporting these programs.

Item

Cerebral Palsy. - The Committee notes that NIH funding for research on cerebral palsy has long been disproportionately low compared with that of similar diseases that affect fewer people. The Committee urges NIH to put a higher priority on cerebral palsy in fiscal year 2013. (p. 100)

Action taken or to be taken

NIH is committed to supporting research to understand, treat, and prevent cerebral palsy. This support, through investigator-initiated grants, broad programs and networks, studies in intramural laboratories, and training and career development awards, is leading to important advances and opportunities for future investments. NIH determines research priorities based on both disease burden and an assessment of how best to bridge knowledge gaps and capitalize on scientific opportunities. NIH continually evaluates what is known and what needs to be known to advance an area forward. However, the specific amount of NIH funding for any disease depends largely on the extent of high-quality research proposed by the scientific community, which reflects the state of science in a given field. If research findings suggest promising hypotheses for understanding, preventing, or treating cerebral palsy, proposals to test these hypotheses may be submitted to NIH and funded, if found scientifically meritorious in peer review. If knowledge gaps are too wide or investigators lack critical tools, more basic discovery research may be required. Breakthroughs leading to new hypotheses or innovative approaches to hard problems can come, sometimes unpredictably, from a wide range of basic science. Thus, broad NIH support for basic research is also essential to ultimately decreasing the burden of cerebral palsy.

Premature birth is associated with an increased risk for brain injuries that cause cerebral palsy, including asphyxia, in which a lack of oxygen can damage the brain. An NINDS-funded clinical trial through the NICHD Maternal Fetal Medicine Unit Network previously showed that magnesium sulfate—an inexpensive, easily prescribed drug—significantly reduced the risk of cerebral palsy when given to pregnant women prior to a premature birth. NINDS also supported planning for a potential trial to test whether early intervention with erythropoietin, a hormone shown to be protective in animal models of brain injury, will improve neurological outcomes, including cerebral palsy, in extremely low birth weight infants. Ongoing basic, translational, and clinical research, including studies at two multi-institutional centers, focuses on understanding brain injury and recovery after perinatal oxygen deficiency in full term and premature infants,

developing treatments for neonatal brain injuries, and identifying risk factors and biomarkers for adverse neurological outcomes. Biomarkers, or measurable indicators of disease risk or progression, could provide a rationale for targeting high-risk infants in clinical trials for prophylactic or therapeutic interventions. For those already affected by cerebral palsy, NINDS funds efforts to improve communication devices and characterize joint control and brain function related to motor deficits. Finally, broad NINDS programs are available for future cerebral palsy research, such as the Cooperative Program in Translational Research, which supports milestone-driven treatment development; and NeuroNEXT (Network for Excellence in Neuroscience Clinical Trials), a new network for early stage clinical trials in any neurological condition.

NICHHD and the NIH Clinical Center (CC) also invest in research to understand cerebral palsy and develop interventions. CC investigators are seeing dramatically improved walking ability in children with cerebral palsy in a study on the effect of exercise using an elliptical trainer. In other recent advances, a study by NICHHD's Neonatal Research Network provided further evidence that a special cooling method increases survival from birth asphyxia without increasing the risk for long-term disability; and NICHHD intramural researchers showed, in a rabbit model of cerebral palsy, that an anti-inflammatory drug delivered using nanotechnology improved movement ability. NICHHD's National Center for Medical Rehabilitation Research also continues to support research to improve function in people with cerebral palsy, with projects on gait, motor control and spasticity, modeling movement, and orthotic, pharmacological, and surgical interventions.

Item

Chimpanzees. - The Committee commends NIH for adopting the IOM's recommendations regarding research involving chimpanzees in the December 2011 report "Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity." The IOM found that chimpanzees are "largely unnecessary" for current research. One possible exception cited by the IOM is efficacy testing of a prophylactic hepatitis C vaccine, but the report pointed to several alternatives which are currently in development that could eliminate any need for chimpanzees in this type of research. The Committee urges NIH to put a priority on developing these alternatives. (p. 100)

Action taken or to be taken

NIH will continue to take every opportunity to support the development of alternatives to the use of chimpanzees as well as other species in research. One high profile, alternative model effort supported by NIH is in the field of hepatitis C virus (HCV) infection, an area of research that for many years relied almost exclusively on the use of chimpanzees. The alternative model approach showing the most potential in the area of HCV research (and referenced in the Institute of Medicine report) is the use of humanized mice. NIH-funded scientists have developed ways to successfully transplant pieces of human liver into mice. This development is important to HCV research because mice ordinarily cannot be infected with HCV. Research is showing, however that humanized mice may be a useful small animal model for HCV disease. These mice, rather than chimpanzees, could then be exposed to drug candidates to determine safety and efficacy. ("*Humanized mice with ectopic artificial liver tissues,*" by Alice A. Chen, et al. *Proc Natl Acad Sci U S A.* 2011 July 19; 108(29): 11842-11847.) In related efforts, NIH-funded

scientists have identified, in the mouse, a network of molecules that interact and play a critical role in HCV cell entry. Entry is a necessary prerequisite for infectivity. Preventing cell entry would block an essential step in the viral life cycle and would therefore prevent infection. Instead of using a chimpanzee (or other non-human primate model) to study HCV, the humanized mouse model may help to answer the same questions currently answered by chimpanzees (“*Hepatitis C virus host cell entry*,” by Ploss A. *et al. Current Opinion in Virology* 2012, 2:14–19). These efforts have the near-future potential of replacing or reducing the use of chimpanzees to answer HCV-related questions and relieve a major and expensive bottleneck in the drug discovery pipeline.

In addition to developing and validating genetically engineered animals (such as the humanized mouse), NIH will continue to support the development and validation of other technologies that allow researchers to employ alternatives to chimpanzees. These technologies include, for example, three-dimensional cell/tissue/organ culture approaches that mimic the function of human organs (e.g., the current NIH/DARPA/FDA tissue chip initiative, which accurately models the structure and function of human organs such as the lung, liver and heart <http://www.nih.gov/news/health/jul2012/ncats-24.htm>), and the use of computational science to explore the potential for computer models.

Item

Class B Animal Dealers. - The Committee commends NIH for moving to end the use of Class B random source dealers as suppliers of dogs and cats to its grant recipients by recently announcing a ban, effective October 1, 2012, on the acquisition of cats from Class B random source dealers. The Committee urges NIH to implement the ban on the acquisition of dogs from Class B random source dealers no later than 2015 and requests an update on this matter in the fiscal year 2014 congressional budget justification. (p. 100-101)

Action taken or to be taken

In FY 2011 NIH developed and implemented a pilot program that supports establishment of a USDA licensed Class A vendor resource with a breeding capacity to provide sufficient numbers of mature, large, socialized, out-bred hounds or mongrel research dogs to replace dogs now acquired through Class B dealers. With the opportunity to establish new USDA licensed Class A breeding colonies, and the time necessary to breed, whelp, wean, socialize, and raise animals to a size and age necessary for research purposes (approximately 2 years), the phase-in must be done over a period of several years. In this transition from Class B to Class A-purpose bred dogs it is critical to validate the scientific suitability of the animals provided through this contract to ensure that the important scientific research is not harmed or jeopardized. The acquisition began with a small number of animals available for evaluation of scientific suitability. To date, the number of animals has increased each year with a majority of animals expected to be available in FY 2014. It is anticipated that this scaled-up resource as well as other 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 research animals provided by Class B vendors and

encouraging researchers to begin planning for this transition as soon as possible. This policy statement indicated that full transition and evaluation would be completed in 3-4 years. At that time a final policy statement will be issued and NIH will not allow NIH research funds to purchase dogs from Class B dealers. Additionally NIH will provide training to extramural staff regarding the transition in policy and how to access Class A dogs. On February 8, 2012 NIH issued a policy statement for the research community (NOT-OD-12-049) informing them of a ban on the purchase of cats from Class B dealers effective October 1, 2012.

At this time NIH does not have sufficient information from the pilot program to assess the scientific suitability of the dogs provided through the Class A vendor under contract for this acquisition. The number of contract-procured animals has grown. In 2013 the contract animals will be allocated to a broader number of researchers with particular oversight given to socialization and conditioning necessary for their scientific suitability in a diversity of research protocols.

Item

Collaboration With DOE. - The Committee commends NIH and DOE's national laboratories for their collaboration on research and development projects, which have resulted in advances in bioinformatics and breakthroughs in atomic resolution structural biology. The Committee encourages the Director and ICs to continue these collaborations. (p. 101)

Action taken or to be taken

There continues to be widespread collaboration between the National Institutes of Health (NIH) and the Department of Energy (DOE). There are areas of science that are relevant to both that benefit from cooperative discussion, planning, and funding activities. Collaborations include those among staff at several NIH Institutes and Centers and DOE Offices.

NIH and DOE have formed a NIH/DOE Nuclear Medicine Working Group to address two issues of planning: (1) the availability of research isotopes; and (2) the training of radiochemists. To address the first issue, a trans-NIH committee, coordinated by the National Institute of Biomedical Imaging and Bioengineering (NIBIB), worked together to identify and prioritize radioisotopes necessary for biomedical research, and estimate annual quantities.

To address the second issue, NIBIB continues collaboration with DOE on a radiochemistry program of excellence and training. In 2012 additional funds were provided to supplement the training component, and in 2013 DOE and NIBIB will issue a joint funding opportunity announcement for the training of radiochemists.

The cooperative stewardship of synchrotrons shared by NIH and DOE has led to breakthroughs in atomic resolution structural biology. NIH continues planning to build and operate beamlines at the National Synchrotron Light Source-II (NSLS-II). This new DOE synchrotron facility will replace the existing NSLS at Brookhaven National Laboratory (BNL). Experimental facilities at NSLS-II will provide an X-ray beam that will deliver greater efficiency and will allow interrogation of more challenging specimens than currently possible at other synchrotrons. The goal is to become fully operational in 2015, and access to these beamlines will be available to all

investigators beginning in 2016. This project is led by the National Institute of General Medical Sciences (NIGMS) with participation by NIBIB, the National Institute of Allergy and Infectious Diseases (NIAID) and the National Cancer Institute (NCI) at NIH as well as the DOE Office of Biological and Environmental Research (BER), and Office of Basic Energy Sciences (BES), which is building the synchrotron.

Additional ongoing collaborations between DOE/BER and various NIH Institutes and Centers continue, including the NIGMS Biomedical Technology Research Centers (BTRCs). NIGMS supports 10 BTRCs located at 6 different National Labs, at a cost of \$20 million annually. The technologies and expertise in these centers is applied to over \$200 million/year of NIH-funded projects, through collaborations between the centers and NIH-supported scientists. Every BTRC is a unique resource, providing access to advanced capabilities that enable biomedical researchers to attack problems that would otherwise be beyond their reach.

NIGMS also provides funds to supplement DOE/BER awards and DOE/BES activities at the DOE funded Stanford Synchrotron Laboratory, the Advanced Light Source, the National Synchrotron Light Source and the Advanced Photon Source. These supplemental funds allow for enhanced user access by NIH-funded biomedical researchers.

Item

Collaboration With the FDA. - The Committee commends NIH for its participation in a NIH–FDA Joint Leadership Council to help ensure that regulatory considerations form an increasing component of biomedical research planning and that the latest science is integrated into the regulatory review process. The Director is urged to continue this joint effort to advance the translation of biomedical research discoveries into approved diagnostics and therapies as well as promote science to enhance the evaluation tools used for regulatory review. (p. 101)

Action taken or to be taken

Improving the translation of biomedical research discoveries into new approved diagnostics and therapies is a top priority for NIH. NIH and FDA will continue to work together strategically to tackle high priority issues of common interest and to enhance the evidence-based knowledge and evaluation tools used for regulatory review. Accordingly, the NIH-FDA Joint Leadership Council will continue to serve as a forum for our agencies to work together to advance our common goal of improving public health by promoting the translation of basic and clinical research findings into medical products and therapies. Toward that end, pairs of Council members, one each from NIH and FDA, selected projects and developed working groups consisting of senior level agency staff with relevant subject matter expertise to advance projects in each of the priority areas of preclinical research, clinical research and trials, drug rescue and repurposing, tobacco science, and joint training and education.

Many of the projects and associated initiatives were started in 2011 and will continue into the future. For example, the Leadership Council’s Tobacco Science Working Group developed research initiatives and funded a number of projects including a longitudinal tobacco cohort study. The findings derived from these activities will provide FDA with a scientific evidence base as the agency continues to develop and apply its new regulatory authority over tobacco

products. The Leadership Council also supported a new project to develop microphysiological systems for testing drug efficacy and toxicity, a project that will continue for the next several years in partnership with the Defense Advanced Research Projects Agency.

In 2013, the research projects awarded through the Joint Leadership Council's early initiative (*Advancing Regulatory Science Through Novel Research and Science-Based Technologies*) funded and supported in large part by the NIH Common Fund, are planned to come to completion. The findings and development of new tools, approaches and methodologies, such as in the area of adaptive clinical trial design, are expected to facilitate further research and regulatory activities.

In addition to the Joint Leadership Council activities, NIH Institute and Center staff participate in NIH-FDA working group activities that are either disease or project focused in areas such as nanotechnology, patient-reported outcome measures, novel technologies to assess toxicology (to improve new drug risk assessment), biomarker identification (for Alzheimer's Disease and other diseases), or on the science of small clinical trials and rare diseases. Moreover, the Cures Acceleration Network program offers another opportunity to advance future NIH-FDA collaborations to ensure that regulatory considerations are incorporated into the scientific process and that the science builds an evidence-base for regulatory decision making.

Item

Congenital Muscular Dystrophy. - The Committee applauds NIH for its growing support of congenital muscle disease research, particularly in congenital muscular dystrophy and congenital myopathy, which will yield returns across the muscular disorders. The Committee also commends NINDS and NIAMS for its financial support of scientific conferences to identify common therapeutic targets and action plans toward clinical trial readiness. The Committee urges NIH to continue supporting grants and other funding mechanisms to advance key congenital muscle disease initiatives for clinical trial readiness and requests an update in the fiscal year 2014 congressional budget justification on total dollars spent on congenital muscular dystrophy and congenital myopathy research. (p. 101)

Action taken or to be taken

NIH supports a wide portfolio of research on the muscular dystrophies, including congenital muscular dystrophy (CMD) and congenital myopathy. In FY 2012, NIH spent approximately \$6.7 million on Congenital Muscular Dystrophy research and \$5.4 million on Congenital Myopathy research. The NIH-funded Paul D. Wellstone Muscular Dystrophy Cooperative Research Center at the University of Iowa focuses on the group of disorders known as dystroglycanopathies, which include the CMDs. Research efforts at this Wellstone center include mechanistic and preclinical therapy development studies, as well as the development of clinical trial infrastructure in CMD. The research cores of this Wellstone center provide patient diagnostic testing and a national tissue and cell culture resource.

The CMDs are multi-system disorders that impact the central nervous system in addition to the musculature. An award funded by the American Recovery and Reinvestment Act to the University of Iowa has supported studies of a subtype of CMD to further understand how the

deficiency in a certain protein modification mechanism leads to muscle wasting and brain abnormalities. The project used high-throughput screening approaches to identify small molecule therapeutics to treat CMDs. Additional projects funded by NIH are studying the mechanisms underlying the brain malformations in CMD and the role of genetic mutations in rare forms of myopathy, as well as evaluating the feasibility of certain therapeutic agents. Researchers recently published the results of an NIH-supported study, which demonstrated that one protein (laminin-111) is effective at reducing the pathology and increasing the lifespan in a mouse model for a specific type of CMD.

NIH continues to encourage research aimed at developing therapies for these and other dystrophies. NINDS worked with CureCMD to establish common data elements for CMD as part of the larger NINDS Common Data Elements (CDE) project. Common data elements ensure that data is consistently captured and recorded across clinical studies and trials and are important to have in place as therapies move to the point of clinical trial readiness.

In April 2012, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Neurological Disorders and Stroke (NINDS), the National Center for Advancing Translational Sciences (NCATS), and the NIH Office of Rare Diseases Research (ORDR) sponsored the scientific conference entitled, “Congenital Muscular Dystrophy: From Clinical Pathology to Underlying Scientific Mechanisms, Exploring the Role of the Myomatrix.” The meeting brought together basic scientists, clinicians, advocacy groups and pharmaceutical industry representatives from diverse fields to discuss and evaluate the contributing mechanisms of the myomatrix -- a collection of proteins and other molecules that surround and interact with the surface membrane of muscle cells, and contribute to the underlying clinical pathology relevant to the quality of life and life span of patients with congenital muscular dystrophies.

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. The Committee supports further research regarding treatments that target the underlying cause of CF, building upon the success of the recently approved new drug Kalydeco. The Committee encourages support for protein structural studies that may advance the understanding of mechanisms of action of CF drugs in clinical development and also 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. 101)

Action taken or to be taken

Identifying therapies to reduce the burden of illness and extend the life expectancy of CF patients remains a top priority of NHLBI. The Institute supports a vigorous basic and clinical research program promoting better understanding of the underlying pathophysiology of CF and discovery of improved treatment options. Key questions about pathogenetic mechanisms are being

answered, and new disease models in large animals as well as mice are providing new opportunities for research and therapeutic development.

Whereas the search for treatment advances had been largely focused on established disease in older children and adults, the availability of newborn screening has now extended its scope to prevention of CF lung disease earlier in life. NHLBI recently released a funding opportunity announcement to solicit applications designed to explore mechanisms involved in the onset, progression, and severity of lung disease in infants and young children with CF; included is a call for research to develop innovative biomarker and imaging approaches to assess structural changes and physiologic function. The new knowledge that emerges from this initiative may be important to the design of clinical studies testing therapeutics to prevent the onset and progression of CF lung disease.

CF is caused by an error in the gene that provides instructions for making a protein called CFTR (CF transmembrane conductance regulator), which controls the flow of water in tissues and thereby enables production of free-flowing mucus. An emerging field in CF therapy is development of treatment strategies targeting the basic defects in protein structure and function, instead of just their symptomatic manifestations. Small molecule “corrector” and “potentiator” drugs that partially reverse the CF genetic defect or improve function of CFTR have shown promise in early-stage clinical trials. Because these new drugs currently address only a small subset of CF patients with a specific CF mutation, NHLBI recognizes the opportunities for additional research to explore their utility in patients with other mutations and in combination with other therapies so that optimal treatments for the wide range of individual patients can be identified. Further structural and functional studies of CFTR are important for the continued development of new therapies and was an area of focus in an NHLBI workshop on protein structure and lung disease held in November 2012.

CF shares pathophysiologic mechanisms with other major human airway diseases such as chronic obstructive pulmonary disease (COPD). For instance, mucus obstruction and dehydration contribute significantly to the evolution of both diseases, and accumulating evidence suggests that CFTR may play a role in COPD, as happens in CF. Agents that reverse the basic defect in CF patients may constitute a new therapeutic strategy in COPD patients. Hence, research on CF may provide valuable insights into the pathogenesis and treatment of other, more common, chronic airway diseases.

Item

Doctors of Veterinary Medicine [DVMs] and Loan Repayment Programs. - The Committee recognizes the important role that DVMs play in the biomedical research enterprise because of their background and training in disease processes across all animals, including cross-species virus transmission, and animal models. As with other medical professionals, large debt upon graduation influences their choice to pursue careers in biomedical research. DVMs participate on clinical research teams and are eligible in that capacity for loan repayments under the Clinical Research and Clinical Research for Individuals from Disadvantaged Backgrounds loan repayment programs. NIH is encouraged to make this information more widely known to potential applicants, ICs, and reviewers. (p. 101-102)

Action taken or to be taken

NIH has taken steps to communicate to DVMs their eligibility for the Loan Repayment Program. In July 2012, specifics regarding the loan repayment program were made publicly available in the *NIH Guide* (“Extramural Loan Repayment Program for Clinical Researchers (LRP-CR)” at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-123.html> and “Extramural Clinical Research Loan Repayment Program for Clinical Researchers from Disadvantaged Backgrounds (LRP-IDB)” at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-124.html>).

Additional information about the eligibility of DVMs for loan repayment is posted on the NIH web site (http://www.lrp.nih.gov/eligibility/eligibility_of_individuals.aspx). On August 3, 2012, staff from the Division of Comparative Medicine in the Office of Research Infrastructure Programs (ORIP) in the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) discussed the loan repayment program with participants at the Meriel-NIH National Veterinary Scholars Symposium. DPCPSI/ORIP will continue to provide information on the eligibility of DVMs for loan repayment to organizations and academic institutions/departments that are closely associated with veterinarians and veterinary training for distribution to their constituencies and stake holders via websites and newsletters. These organizations include: the Association of American Veterinary Medical Colleges (AAVMC); the American Veterinary Medical Association (AVMA); the Institute for Laboratory Animal Research (ILAR); the Deans of the U.S. Veterinary Colleges Program Officials from NIH Institutes and Centers that have funded training programs that are specifically dedicated to veterinary training; and, Directors of Departments of Comparative Medicine.

Item

Down Syndrome. - The Committee commends NIH for its ongoing efforts to implement the NIH Down Syndrome Research Plan and for establishing the NIH Down Syndrome Consortium, which is focused on facilitating a dialogue between trans-NIH Institutes and the Down syndrome patient community. Increased Federal funding for translational research is important, and investing in Down syndrome-centered research has the potential for benefiting many other diseases and conditions such as Alzheimer’s disease. The Committee encourages NIH to increase the amount invested in investigator-driven research grants and plan for the development of the Down syndrome clinical database, research registry, and biobank. NIH is also urged to establish workshops and mentoring programs to encourage young researchers and scientists to successfully pursue NIH grants for Down syndrome research. (p. 102)

Action taken or to be taken

Down syndrome comprises a set of developmental and physical symptoms that result from having an extra copy of Chromosome 21. NICHD supports research on Down syndrome across life’s stages, which is particularly important now that people with Down syndrome are living longer than ever before. Studies include research on the basic risk factors for this condition, interventions to reduce or ameliorate symptoms, including behavioral and social science research, and possible treatments. Through the NIH Down Syndrome Working Group, NICHD partners with other NIH Institutes and Centers to support and conduct a wide range of research, such as determining which of the extra genes on Chromosome 21 are responsible for cognitive deficits in Down syndrome, and achieving a better understanding of the link between Down

syndrome and Alzheimer's disease. NINDS-funded studies focus on defining which genes cause cognitive impairments, on mechanisms involved in Alzheimer's disease-like pathology, and on aspects of neuronal development and function relevant to Down syndrome, all of which may help identify new treatment targets. For example, one project, co-funded by NINDS and NICHD, which is still in the early stages, is aimed at developing a potential new drug therapy for Down syndrome to improve learning and memory. In another study, funded by NICHD, scientists reported that telomeres (the end regions of chromosomes) are shorter in people with Down syndrome who also have Alzheimer's or similar cognitive impairments, compared with people who only have Down syndrome; they are now exploring whether telomere length could serve as a biomarker for early stages of dementia in individuals with Down syndrome.

Over the last five years, NICHD has funded new research projects with funds from the American Recovery and Reinvestment Act and other dollars, renewed its major animal and tissue repositories for use by researchers across the country, sponsored scientific workshops and meetings, and increased its public outreach and dissemination, generating numerous publications in peer-reviewed journals. In September 2012, NICHD awarded a contract to establish a new Down syndrome patient registry, which will facilitate contacts between individuals with Down syndrome, families, and researchers. Participating individuals may give permission to be contacted by clinicians and researchers to see if they are interested in being recruited into a research study on Down syndrome, potentially allowing research to advance more quickly. NIH also is taking a number of steps to support and encourage the scientific community to submit applications and expand research efforts in this field. NINDS supports training for research on neurodevelopmental disabilities, including Down syndrome and other disorders, through a training program for pre- and postdoctoral fellows based at the Children's Hospital of Philadelphia and the University of Pennsylvania. NICHD has issued a series of funding opportunity announcements seeking research grant applications on understanding and treating co-morbid conditions in adolescents with Down syndrome, and other issues faced by adolescents and their families as they transition to adulthood.

In September 2011, NICHD facilitated the establishment of a public-private Down Syndrome Consortium. The NIH Down Syndrome Working Group has joined with eight national organizations whose missions focus on Down syndrome to foster the exchange of information on biomedical and behavioral research on this condition, explore the establishment of a contact registry for families, and update the NIH Down syndrome research plan, among other collaborative activities. Individuals with Down syndrome and family members are represented on the consortium. A Request for Information was issued by NICHD in August 2012 to invite the Down syndrome community (researchers, health care providers, and patient advocates) to comment on the progress made since the 2007 NIH Down Syndrome Research Plan was released, on existing research gaps that remain, and to provide input on research priorities for NIH.

Item

Drug Allergy. - The Committee is concerned about the incidence of allergic reactions to drugs for debilitating and potentially fatal diseases including cancer, HIV/AIDS, cystic fibrosis, and rheumatoid arthritis. The Committee requests an update in the fiscal year 2014 congressional

budget justification regarding ways in which NCI, NHLBI, NIAMS, and other relevant Institutes can collaborate with NIAID to support research on desensitization of patients who have allergic reactions to potentially life-saving medications. (p. 102)

Action taken or to be taken

NIH, with NIAID at the lead, has a longstanding commitment to basic, translational, and clinical research on allergic and immune-mediated diseases. These efforts have helped to inform our understanding of the mechanisms of allergic reactions, including reactions to medications, and the development of promising prevention and treatment strategies. As part of its efforts to address drug allergy, NIAID is planning a trans-NIH workshop on drug allergy in the spring of 2013. Workshop participants will discuss the state of the science and identify promising areas for future research and research collaborations.

The potential for allergic reactions to essential medications for autoimmune diseases, HIV/AIDS and cancers, remains a particular concern. Drug allergy can be mediated by immunoglobulin E (IgE) as well as non-IgE mediated mechanisms. Desensitization to drugs can, in some cases, be achieved through administration of gradually increasing doses of the offending drug. Successful desensitization results in a reduced allergic reaction on subsequent exposure. Desensitization also has been studied extensively for other IgE-mediated allergies including reactions to pollens, insect venoms, and foods. Recent publications suggest that desensitization is also effective in some cases of non-IgE mediated drug allergy. It is likely that desensitization in food allergy and drug allergy occurs by similar mechanisms. Further research to better understand the mechanisms of desensitization for a variety of allergens can help to inform treatment of allergies, including allergies to potentially life-saving medications.

NIAID will continue to work with other NIH Institutes and Centers (IC), to increase our understanding of drug allergy and to develop strategies to prevent and treat it. NIH carefully monitors patient response to drugs in sponsored trials and monitors the scientific literature for developing trends. The ICs will continue to collaborate to address emergent issues and research opportunities in these areas.

Item

Duchenne Muscular Dystrophy. - The Committee is aware of multiple governmental and nongovernmental efforts to develop patient registries containing valuable data from patients with Duchenne muscular dystrophy. Such registries are critically important to continue advancing Duchenne public health and research projects, but the Committee is concerned about the lack of coordination and potential duplication of efforts. The Committee encourages NIH, working through the Muscular Dystrophy Coordinating Committee and with the private organizations that predominantly fund these registries, to convene a meeting to discuss coordination of all the Duchenne patient registries to the extent possible. The Committee requests an update on this topic in the fiscal year 2014 congressional budget justification. (p. 102)

Action taken or to be taken

While NIH supports a robust portfolio of research in Duchenne Muscular Dystrophy (DMD), it currently does not provide funding for patient registries in this disease. NIH is aware, however,

of the multiple efforts to develop DMD patient registries and the need to ensure consistency and lack of duplication. As the organizing agency of the Muscular Dystrophy Coordinating Committee (MDCC), NIH will convene a discussion of registries for the muscular dystrophies at the next MDCC meeting, planned for August 2013. The MDCC includes representatives from the groups currently involved in the development and maintenance of registries as well as representatives from federal agencies involved in muscular dystrophy research.

NIH recognizes the importance of patient registries since they can serve as resources for the recruitment of patients for natural history studies and clinical trials. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) currently supports several natural history studies that complement the information that is gathered through DMD registries. One project seeks to validate the potential of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) to monitor disease progression and serve as a surrogate outcome measure for clinical trials in DMD. A similar effort is assessing the value of other noninvasive monitoring techniques in children with DMD. These studies could lead to significantly faster and more efficient clinical trials, thus helping to speed the identification of therapies for this disease.

An effort by the National Institute of Neurological Disorders and Stroke (NINDS) – the NINDS Common Data Elements Project – is also aimed at ensuring that appropriate tools are in place as therapies move to the point of clinical trial readiness. Common data elements (CDEs) ensure that data is consistently captured and recorded across clinical studies. CDEs are being developed for neuromuscular diseases in general as well as specifically for DMD. These are both expected to be finalized in early 2013. The Muscular Dystrophy Association is already planning to adopt these CDEs for use in their DMD clinics and clinical registry.

Other research and resources funded by NIH also complement the information collected by registries and – like registries – will help move potential therapies into clinical trials. The Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs) include repositories of research data and biologic resources from patients with different types of muscular dystrophy as well as cores dedicated to patient diagnostic testing. The MDCRCs are also addressing clinical trial readiness to ensure that sufficient tools (e.g., biomarkers, trial endpoints) and knowledge (natural history) are in place. Building upon the work of the Cooperative International Neuromuscular Research Group, an integrated network of clinical study sites, a project newly funded by NIAMS seeks to discover and validate sensitive and specific serum biomarkers for DMD. In addition, scientists are testing the effectiveness of new clinical outcome measures that could be used as primary clinical endpoints by industry and academics in future therapeutic trials of promising new treatments.

As active members of the MDCC, the NIH Institutes with primary responsibility for research on DMD – NINDS, NIAMS, NICHD, and NHLBI – would be pleased to play a key role in discussions about coordination of DMD registries and ways that NIH activities can help enhance these efforts.

Item

Eating Disorders. - The Committee continues to be concerned about the alarming effects of eating disorders on women's health including elevated mortality rates and associated health consequences, such as serious cardiac conditions, kidney failure, gastrointestinal disorders, and osteoporosis. The Committee urges NIH to expand, intensify, and coordinate its activities with respect to research on eating disorders and to examine the possibility of creating collaborative consortia on eating disorders research with a specific emphasis on basic and clinical investigations into the causes, diagnosis, and treatment of these conditions. The Committee requests an update on this topic in the fiscal year 2014 congressional budget justification. (p. 102)

Action taken or to be taken

The National Institutes of Health (NIH) is committed to the understanding, treatment, and prevention of eating disorders, and shares the Committee's concerns with respect to the elevated mortality and health consequences associated with eating disorders. Eating disorders are severe disturbances in eating behavior, such as extreme reduction of food intake or extreme overeating, often accompanied by distress and excessive concern about body weight. They include anorexia nervosa, bulimia nervosa, and binge eating disorder.

The National Institute of Mental Health (NIMH), which serves as the lead Institute for eating disorders research, will consult with other relevant NIH Institutes and Centers (IC) regarding the formation and expected outcomes of a trans-NIH consortium for eating disorders and their associated health consequences.

Currently, NIH manages eating disorders research by assigning applications to ICs based on the scientific focus as it corresponds to the specific mission and scientific expertise of the IC. For example, NIMH supports research projects focusing on the biology, psychopathology, treatment, services, and prevention of eating disorders, as well as studies focusing on understanding suicide risk among people with eating disorders. The National Heart, Lung, and Blood Institute supports scientific studies to understand the effects of eating disorders on cardiovascular health. Research investigating the impact that eating disorders have on the family as a whole is supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).

In recognition of the public health significance of eating disorders and their disproportionate impact on the health of women and girls, an eating disorders scientific workgroup was convened as part of the development of the trans-NIH Strategic Plan for Women's Health and Sex Differences Research.¹⁵ The published workgroup report identifies research gaps and makes recommendations for new research priorities for eating disorders.

NIMH has focused its research on the mechanisms of eating disorders, especially anorexia nervosa, which is the most fatal eating disorder. Recent projects have focused on the genetics and brain changes associated with anorexia as well as its treatment. In a randomized controlled treatment trial, the outcomes of teens with anorexia nervosa appear much better if parents are included, rather than excluded, from the treatment. With this family-based treatment approach, 50 percent of teen participants continued to experience full remission one year after the end of

¹⁵ A copy of this strategic plan may be found at: <http://orwh.od.nih.gov/research/strategicplan/index.asp>.

therapy. Additional research is currently under way that incorporates families in the treatment of adults with anorexia.

Item

Eosinophil-Associated Disorders. - The Committee is pleased that a NIAID working group is developing a research agenda on eosinophilic disorders. The Committee requests an update in the fiscal year 2014 congressional budget justification regarding programmatic initiatives being undertaken based on the working group's recommendations. In addition to NIAID and NIDDK, the Committee urges NHLBI, NICHD, NIMH, and other relevant Institutes to participate in these efforts. Further, NIH should seek opportunities to collaborate with private sector organizations on this initiative. (p. 102-103)

Action taken or to be taken

During the past year, NIAID coordinated the National Institutes of Health Taskforce on the Research Needs of Eosinophil-Associated Diseases (TREAD), a working group of academic investigators and representatives from NIAID, NCI, NIDDK, and NHLBI. The TREAD met monthly by teleconference to identify research opportunities on eosinophilic disorders; in June 2012, NIH held a workshop. Pursuant to these activities, the TREAD outlined the basic and clinical research opportunities in eosinophilic disorders in the September 2012 issue of the *Journal of Allergy and Clinical Immunology* (<http://www.ncbi.nlm.nih.gov/pubmed/22935587>). In addition to the TREAD, NIAID continues its trans-NIH, academic, and private sector organization collaborations to support basic and clinical research on eosinophilic disorders.

As part of a broad effort to expand understanding of eosinophilic disorders, NIAID supports several research projects on eosinophilic esophagitis (EoE). NIAID's Asthma and Allergic Diseases Cooperative Research Centers conduct research on the pathogenesis of EoE. In addition, NIAID-supported investigators recently completed a pilot clinical trial to determine the efficacy of swallowed glucocorticoids for the treatment of EoE; data from this study are being evaluated. NIAID-funded scientists also continue their efforts to develop non-invasive diagnostic tools for eosinophilic gastrointestinal disorders (EGIDs) to reduce the need for invasive endoscopies and biopsies.

The NIAID- and NIDDK-supported Consortium of Food Allergy Research (CoFAR) works to develop new approaches to treat and prevent food allergy, including investigations on the genetic factors underlying the mechanisms of food allergy-associated EoE, and research on EGIDs. NIDDK also supports a portfolio of basic, translational, and clinical research on the causes and treatment of EGIDs to better understand these disorders and to improve diagnosis and treatment for adults and children. For example, researchers are developing a national patient registry to catalog clinical, pathologic, and translational outcomes for individuals with EGIDs. The Registry for Eosinophilic GastroIntestinal Disorders (REGID) is a collaboration of medical centers, health professionals, families, and individuals to improve the knowledge, research, and outcomes for people living with EGIDs (<http://regid.org/>).

NIAID intramural scientists are following a cohort of more than 250 patients with eosinophilic disorders ranging from benign eosinophilia to eosinophilic leukemia. Clinical samples are

collected to examine the role of eosinophils in the various disorders. Investigations include an NIAID-NIDDK collaboration to characterize immune cells in patients with EGIDs; an NIAID-NCI partnership to develop biomarkers for hypereosinophilic disorders; and an NIAID-NHLBI collaboration to evaluate diagnostic imaging for cardiac pathology in eosinophilic disorders. Other NIAID intramural research on eosinophilic disorders includes clinical trials of immunodulatory agents, monoclonal antibodies, and tyrosine kinase inhibitors that target eosinophils.

Item

False Positives and Replications. - The Committee supports NIH's effort to develop a consensus on the issues of false-positive research results. This effort will encourage policies on the publishing of replications (and nonreplications) of previous research and advance scientific knowledge. (p. 103)

Action taken or to be taken

Science is an iterative process where progress is made by experimenting, following-up on new insights, and building upon them. There are a number of initiatives under way to improve the reproducibility of research results, including programs to facilitate data sharing, to standardize research data vocabularies, methodologies, and reporting measures, and to develop new validation tools, technologies, and approaches.

Since successful experiments are more likely to be published, the literature can sometimes give an incomplete picture of the strength of a particular finding. Data sharing is one of the most important ways to strengthen research findings because it enables investigators to have a more complete picture of what is known in a particular area, and it permits others to re-analyze data and to replicate analyses when datasets are sufficiently large. In addition to encouraging data sharing through NIH policy, the agency also is creating an infrastructure of information technologies and databases to facilitate data sharing. For example, the database of Genotypes and Phenotypes (dbGaP) was developed to make data from genome-wide association studies more broadly available. For data on clinical trials, the NIH repository ClinicalTrials.gov is a registry of NIH funded and private sector clinical trials that, through the enactment of the Food and Drug Administration Amendments of 2007, now also contain summary study results for certain clinical trials. While the law does not apply to all clinical trials, as a matter of policy, NIH encourages registration and results submission for all NIH supported clinical trials.

In addition to supporting databases that enable data sharing, NIH is working to improve the usability and comparability of shared data by developing common data standards and definitions across different studies. For example, the NINDS Common Data Elements project aims to help clinical investigators meet high standards, in part, through common data definitions and elements across studies. The NCI Cancer Data Standards Registry and Repository will make it possible to aggregate and manage large data sets using common definitions and data elements.

NIH is also supporting efforts aimed at developing new tools, technologies, and approaches to enhance the validity of research findings, which will enable greater confidence in the reproducibility of findings. For example, NIH is working with academic and private sector

investigators to improve the target validation process, which is an important part of the medical product development process that helps to identify the biological pathways and structures that will be affected by the medical product. The initiative will apply insights and technologies emerging from basic science research, such as genome-wide association studies, sequencing research, and systems biology, to find and validate biochemical substances, genes, receptors, enzymes, and proteins that may have therapeutic effects. Ultimately, target validation ensures that the drug and medical product development path leads to safe and effective products.

These initiatives are important, but NIH recognizes that there may be additional opportunities for more to be done to enhance the reproducibility of published research findings. For example, NINDS recently issued guidance for investigators emphasizing the importance of rigor, control of bias, and transparency of reporting in research http://www.ninds.nih.gov/funding/transparency_in_reporting_guidance.pdf. The Institute also organized an exploratory meeting with journal editors, academic experts, and investigators whose published findings could not be reproduced. NIH will continue to explore the issue and develop strategies to help investigators optimize scientific study designs and methods to promote validity and encourage reproducibility of study findings.

Item

Fragile X-Associated Disorders. - The Committee commends NIH for the NICHD-led effort to update the NIH Research Plan on Fragile X Syndrome and Associated Disorders in light of the significant progress made toward targeted drug treatments since the plan was published. The Committee urges NIH to fully implement and prioritize the updated goals and objectives. In particular, NIH is encouraged to support translational research that shows significant promise of safer and more effective treatments for Fragile X-associated disorders. The Committee also encourages NIH to work with CDC to support and coordinate Federal investments in data collection efforts related to Fragile X. (p. 103)

Action taken or to be taken

In order to maintain the momentum of discovery and further develop research relevant to Fragile X-associated disorders, NIH is reviewing and updating the *NIH Research Plan on Fragile X Syndrome and Associated Disorders*. The Research Plan was originally developed in 2008-2009, when the trans-NIH Fragile X Working Group of eight NIH Institutes and Centers and led by NICHD, convened working groups composed of scientific experts from the research and clinical communities, representatives of affected individuals and family members, and other pertinent federal agencies. The purpose of these working groups was to generate research goals and objectives for Fragile X syndrome, and the associated disorders of Fragile X-associated tremor/ataxia syndrome (FXTAS) and Fragile X-associated primary ovarian insufficiency (FXPOI). The goals were designed to guide NIH and the Fragile X syndrome, FXTAS, and FXPOI research communities and to be shared with other federal agencies to facilitate coordinated research activities that would lead to timely detection, diagnosis, treatment, and prevention of the targeted disorders.

In 2012, to gather input on the impact of the research plan from the Fragile X community, NICHD solicited information from interested stakeholders via a Request for Information.

NICHD and its NIH partners convened a meeting of leading scientific experts, representatives for affected individuals and family members, and other federal agency representatives, including the CDC and HRSA. Attendees were charged with revisiting the goals and aims of the current plan, reporting on the progress being made toward achieving those goals, and identifying research gaps and potentially exciting new avenues of investigation, including collaborative efforts. A report on these findings is forthcoming.

NIH continues to maintain a substantial and diverse portfolio of Fragile X-related research, including translational research that could lead to potential treatments to improve the lives of individuals with Fragile X and related conditions. These efforts are coordinated by the trans-NIH Fragile X Research Coordinating Group, which includes members from NICHD, NIMH, NINDS, NIA, NIDDK, NIGMS, NCI, and NIDCD.

For example, NICHD-supported researchers currently are studying the “mGluR Theory” of Fragile X: that exaggerated signaling in mGluR (metabotropic glutamate receptor) pathways because of missing Fragile X Mental Retardation Protein leads to the condition’s various symptoms. Following promising results from research in the mouse, in May 2010 a clinical trial of an mGluR5 antagonist began in adults with Fragile X syndrome. If the results from the adult study show promise, the drug can be tested in clinical trials with children. NICHD, through its Best Pharmaceuticals for Children Act activities, will add its support to NIMH as well as other Institutes and Centers and organizations for the pediatric clinical trials. In another promising line of research, scientists have found that a class of drugs called PI3 kinase inhibitors can correct defects in the anatomy of neurons in a mouse model of Fragile X syndrome. These findings suggest that PI3 kinase inhibitors could help improve learning and cognition in individuals with Fragile X syndrome.

NINDS supports a range of studies focusing on signaling pathways and molecular mechanisms that contribute to cognitive impairment, autism, and epilepsy in Fragile X syndrome, and to neurodegeneration in FXTAS. NINDS also administers two projects within an NIH-supported consortium to develop targeted molecular therapies for FXTAS. One is developing animal models for preclinical therapy development, and the other is characterizing cognitive function in children and adults with repeat expansions in the FMR1 gene in the full mutation, premutation, or normal range, as a way to understand how variations in a single gene produce a spectrum of cognitive dysfunction.

In early FY 2013, NICHD, along with NINDS and NIMH, recompleted the *Collaborative Centers for Research in Fragile X* program, which was originally established in response to the Children's Health Act of 2000. Applications are scheduled for review in late summer 2013. Successful Centers will be composed of transdisciplinary teams of investigators working together to facilitate the translation of basic research findings related to Fragile X syndrome, FXTAS, and FXPOI, from bench-to-bedside-to-community.

Item

Glomerular Disease. - The Committee continues to be concerned about the impact of idiopathic nephrotic syndrome [NS] and primary focal segmental glomerulosclerosis [FSGS] within the minority community, particularly given the increasing body of research linking FSGS to gene variants predominately expressed in African Americans. The Committee urges NIMHD to collaborate with NIDDK on NS and FSGS research. The Committee commends ORDR for its support of the Nephrotic Syndrome Rare Diseases Clinical Research Network and recognizes the potential impact of this study for patients with NS and FSGS and their families. Finally, the Committee urges NIDDK to continue to support research on NS and FSGS in order to develop treatments and cures that could ultimately prevent end-stage renal disease. (p. 103)

Action taken or to be taken

Glomerular disease continues to be a priority of the National Institute on Minority Health and Health Disparities (NIMHD) research agenda through its Centers of Excellence Program and the Health Disparities Research program. The project, *APOL1 Variants: Understanding the Basis of Disparities in Rates of Kidney Disease*, supported by the NIMHD R01 grant funding mechanism, stems from the investigators' previous work finding that specific genetic variants in the APOL1 gene account for the very high rate of kidney disease in African Americans, and also confer resistance to Sleeping Sickness in Africa. Specifically, APOL1 kidney disease variants have a major impact on multiple different types of kidney disease including hypertension-associated end-stage renal disease (H-ESRD), focal segmental glomerulosclerosis (FSGS), and HIV-associated nephropathy (HIVAN). This research project is examining the factors that combine with the high risk APOL1 genotype to cause overt kidney disease. Understanding how these differences in the APOL1 gene cause kidney disease in African Americans will have direct implications for improving all aspects of care for the growing number of people with this serious public health problem and for reducing the very large disparity in the rates of kidney disease.

NIDDK encourages research on glomerular diseases in a number of ways. NIDDK's initiative "Grants for Research in Glomerular Diseases," is soliciting studies to enhance understanding of the various primary or secondary forms of glomerular disease, including FSGS. NIDDK, along with the NIH Office of Rare Disease Research, also supports research on glomerular diseases through the Nephrotic Syndrome Rare Diseases Clinical Research Network (NEPTUNE), a multi-site, multidisciplinary collaborative research and education network. NIDDK also supports a robust program of intramural research that has reported important insights into the racial disparities in FSGS in recent years.

In addition, in 2012 NIDDK convened a scientific conference, entitled "Glomerular Disease Pathophysiology, Biomarkers, and Registries for Facilitating Translational Research." This meeting explored practical next steps that might be taken by extramural scientists, the pharmaceutical industry, professional societies, and disease advocacy groups in FSGS and other forms of nephrotic syndrome. As a result of this meeting, NIDDK will issue this fall a new funding opportunity, entitled "Advancing Clinical Research in Primary Glomerular Diseases," that will establish a longitudinal, observational cohort for the collection of genetic, phenotypic, and biochemical data on these diseases.

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 common and rare, and who strive to translate research advances and discoveries into treatments and cures. Furthermore, the Committee recognizes that the national demand for high-quality human biospecimens will continue to grow, as will its importance to advancing translational research across NIH. Therefore, the Committee urges the Director to expand core and trans-NIH support for its nationwide human tissue and organ procurement program. (p. 103)

Action taken or to be taken

The Office of Research Infrastructure Programs (ORIP) in the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) supports the Human Tissues and Organs Resource for Research (HTOR; Philadelphia, PA) Cooperative Agreement. HTOR is a procurement network within the National Disease Research Interchange. This resource supports the procurement, preservation, and distribution of human tissues and organs for basic and clinical research at research centers, academic institutions, NIH, and other federal agencies. An overarching purpose of the research funded by DPCPSI/ORIP is to reduce the burden on society of morbidity and mortality of diverse conditions and diseases and to understand normal human tissue and organ function. With the participation of NEI, NHLBI, NIAID, NIAMS, and NIDDK, DPCPSI/ORIP plans for the continued support and advancement of human organ and tissue resources and has issued a Funding Opportunity Announcement for re-competition (RFA-OD-12-002; (<http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-12-002.html>)). The resource for human organs and tissues will continue to provide a wide variety of human tissues and organs, both diseased and normal, to biomedical researchers. Such samples will include tissues from the nervous system, pulmonary system, cardiovascular system, endocrine system, eyes, skin, bone, and cartilage.

Item

Interstitial Cystitis [IC]. - The Committee commends ORWH for its support of research on IC. The Committee understands that IC disproportionately affects women and encourages ORWH to continue to work with NIDDK to support specialized centers of research that serve as a valuable source of IC research. (p. 103)

Action taken or to be taken

ORWH has worked closely with NIDDK to support research on poorly understood pain conditions that predominantly affect women, including interstitial cystitis/painful bladder syndrome (IC/PBS) and irritable bowel syndrome (IBS). Many women with IC/PBS also have IBS. For over a decade, ORWH and NIDDK have co-funded a Specialized Center of Research focused on IBS and IC/PBS at the University of California, Los Angeles (UCLA), which is led by preeminent scientists in the field of neurovisceral pain studies. This Center recently competed for and was awarded a third phase of funding. During its next phase, the Center will investigate whether sex differences play a role in how the nervous system responds to stress and thereby influence a person's susceptibility to IBS and IC/PBS—information that could help in developing more effective treatments for these conditions. The ORWH has also worked with

NIDDK on other IC/PBS efforts, including, most recently, co-sponsoring an initiative that funded interdisciplinary research teams focused on IC/PBS.

As part of the development of the Strategic Plan, *Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research*, ORWH held a regional scientific meeting that included discussion of chronic pain syndromes. IC/PBS was one of the main conditions discussed, and recommendations from that meeting are part of this report, available at: http://orwh.od.nih.gov/research/strategicplan/ORWH_StrategicPlan2020_Vol2.pdf

The ORWH will continue to work with NIDDK on advancing research that can yield effective therapeutic or preventive strategies for this painful condition that disproportionately affects women.

Item

Lupus. - Given the scope and impact lupus has on virtually every organ system in the body, advances in lupus research require studies that transcend multiple disciplines, including genetics, basic and applied immunology, proteomics, and therapeutics. Therefore, the Committee urges the establishment of a trans-NIH coordinating committee on lupus that could focus on developing a comprehensive NIH research strategy and identifying gaps in lupus research. (p. 104)

Action taken or to be taken

Lupus is an autoimmune disease, one of several disorders of the immune system. Lupus can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Although people with the disease may have different symptoms, some of the most common ones include extreme fatigue, painful or swollen joints (arthritis), unexplained fever, skin rashes, and kidney problems.

NIH supports basic research aimed at identifying novel targets for the use of existing drugs for patients with lupus. Work is also being performed that is laying the foundation for the development of new therapies to treat this disease, some of which are currently in clinical trials. Existing drugs often have a proven safety profile, making them more readily available for patients to begin treatment once their efficacy has been established. One example is the antimalarial medication hydroxychloroquine, which is also used in the treatment of lupus and other autoimmune diseases. NIH-supported research has shown that lupus patients treated with hydroxychloroquine were less likely to develop severe kidney disease, had lower disease activity, and used less steroid medication.

Recent efforts funded by NIH have identified a significant association between disease activity and increased expression of type I interferon, a molecule which stimulates many subsequent, damaging inflammatory pathways. A distinctive “interferon signature” can be detected in the blood of lupus patients, sometimes before the disease develops fully and in advance of a flare of disease activity. Targeting inflammatory pathways may help to prevent disease flares and disease progression.

Clinical trials, supported by NIH, investigated the potential benefits of statin treatment to slow the progression of atherosclerosis (hardening of the arteries) in children with lupus. While the results did not demonstrate compelling evidence to support treatment, there may be benefits to particular patient subgroups with severe disease.

Lupus occurs in women nine times more frequently than in men. NIH-supported scientists studying the influence of X-chromosome genes on lupus risk are opening new avenues for investigation about the female predominance of the disease.

The Lupus Federal Working Group continues to facilitate collaboration among the NIH Institutes and Centers, other Federal agencies, voluntary and professional organizations, and industry with an interest in lupus, with a particular focus on multi-disciplinary studies. The most recent meeting was held in May 2012, where participants representing government and non-government organizations, discussed the impact and utility of the 2007 report entitled, “The Future Directions of Lupus Research”.

Item

Lymphatic Research and Lymphatic Disease. - The Committee commends the trans-NIH Coordinating Committee for Lymphatic Research [CCLR] for its efforts. As the Committee has previously requested, more oversight and engagement are needed by the Director and ICs to help make meaningful advances in research of the lymphatic system and medical care for lymphatic diseases. Furthermore, in keeping with the 2007 CCLR Working Group recommendations, the Committee urges the CCLR to work cooperatively to create interdisciplinary programs to train new investigators, such as an annual primer course for doctoral and postdoctoral candidates. The Committee also expects greater involvement by NIBIB, especially in carrying forth the CCLR Working Group quantitative and molecular imaging recommendations. Finally, the Committee urges NCATS to provide representation to the CCLR. (p. 104)

Action taken or to be taken

NIH has continued to foster research on the lymphatic system and disorders that affect it. The trans-NIH Coordinating Committee for Lymphatic Research (CCLR), with current representation from NHLBI, NCI, NICHD, NIAID, NIDDK, NEI, NIBIB, NINR, NIAMS, and NCATS, serves as a resource and a forum for many activities in this area, included those highlighted below. As noted, CCLR includes representatives from both NIBIB and NCATS, as suggested by the Committee.

NIDDK and NHLBI partnered to release two companion funding opportunity announcements (FOAs) titled Lymphatics in Health and Disease in the Digestive, Cardiovascular, and Pulmonary Systems. The initiative will support studies of lymphatic vessel physiology and pathophysiology related to health and disease of the digestive, cardiovascular, and pulmonary systems; resolution of thromboembolic events; and associated inflammatory and immune responses. NIDDK released another companion FOA, New Technologies for the Study of Lymphatics in the Digestive and Urinary Systems, which encourages small businesses to develop technologies to facilitate research on the lymphatic system.

NHLBI solicited contract proposals for a product-development program for vascular diseases, thrombotic disorders, and pulmonary hypertension—Vascular Intervention/Innovations and Therapeutic Advances (VITA)—with a specific focus on products for detection or treatment of lymphatic disease.

NICHHD issued two FOAs that include specific mention of research on the development of the lymphatic system. The first, Developmental Aspects of Human Structural Birth Defects, is intended to support program projects entailing the integration of basic and clinical/translational approaches to understanding the developmental biology and genetics of congenital structural malformations in a variety of organ systems, including the lymphatic system. The second, Enhancing Developmental Biology Research at Undergraduate Institutions Academic Research Enhancement Award, encourages grant applications to strengthen the developmental biology research environment at non-research-intensive educational institutions that primarily provide baccalaureate degrees.

Leadership from NHLBI, NIDDK, NICHHD, NIAID, and CSR met with representatives of the Lymphatic Research Foundation (LRF) in late 2011 and early 2012 to exchange ideas about NIH-supported research and interdisciplinary training in lymphatic disease. Training opportunities were also discussed at the open session of one of the CCLR meetings. The CCLR members apprised the LRF representatives of type of training opportunities available at NIH including institutional training awards.

The National Lymphatic Disease and Lymphedema Registry has been selected to participate in the Global Rare Diseases Patient Registry, and Data Repository pilot project, which is supported by the Office of Rare Diseases Research, a part of NCATS. The pilot project is focused on helping new registries establish standardized data fields and policies.

Item

mHealth. - New mobile and wireless health technologies, known as mHealth, are likely to have a profound impact on biomedical research and the delivery of healthcare. The Committee applauds OBSSR for leading efforts to systematically evaluate the impact of new technologies. The Committee is pleased that virtually all of the NIH Institutes and NSF are collaborating in this area. (p. 104)

Action taken or to be taken

Mobile and wireless health (mHealth) technologies have developed at an exponential pace in recent years; however, the integration and translation of these cutting-edge technologies into rigorously evaluated health research and healthcare tools have lagged behind. The Office of Behavioral and Social Sciences Research (OBSSR) continues to work with most of the NIH Institutes and Centers (ICs), the National Science Foundation (NSF), and other partners to develop a research infrastructure for mHealth that will allow for efficient, systematic evaluation of mHealth technologies so that these tools have the greatest health impact.

OBSSR in partnership with other ICs is leading the development of a new Funding Opportunity Announcement that will solicit innovative mHealth research projects to validate wireless and

mobile devices in ongoing NIH-funded clinical and observational trials. This competitive supplement announcement will efficiently allow for the validation of mHealth tools by leveraging existing research investments.

In addition, OBSSR has sponsored a range of activities designed to help develop the mHealth research capacity. In the last 15 months, OBSSR has hosted three NIH training institutes to develop multidisciplinary teams to address significant health problems using mHealth technologies. These week-long trainings (http://obssr.od.nih.gov/training_and_education/mhealth/index.aspx) target individuals from diverse scientific disciplines (medical, behavioral and social sciences, engineering and computer sciences), as well as industry. Also involved in the planning and execution of these training institutes were staff-members from NSF, Indian Health Service, Food and Drug Administration, Office of the National Coordinator, and Federal Communications Commission. Because of the high demand from the scientific community, the institute will be offered again in 2013. Moreover, OBSSR will sponsor two new brief training events that will target behavioral and social science health researchers who wish to add mobile technologies to their existing work.

Finally, OBSSR has been very active in stimulating the development of scientific methods to evaluate mHealth technologies. This started with a conference, co-sponsored by the Robert Wood Johnson (RWJ) and McKesson Foundations in August 2011 (http://obssr.od.nih.gov/scientific_areas/methodology/mhealth/mhealth-workshop.aspx), which has since yielded an academic paper for the health research community and another invited paper that is in preparation for the computer science and engineering disciplines. Additionally, OBSSR in partnership with multiple ICs, NSF and the RWJ Foundation, will organize another workshop in 2013 to explore advances in mHealth evaluation methodologies.

Item

Minority Researchers. - The Committee is deeply concerned by the findings of the recent study “Race, Ethnicity, and NIH Research Awards,” which shows a disparity in the rates at which African Americans received NIH R01 grants. The Committee looks forward to the findings of the blue ribbon panel examining this matter. (p. 104)

Action taken or to be taken

NIH expresses an equal concern for the findings published by Dr. Donna Ginther and colleagues in August 2011 in *Science* that detailed a 10-percentage point disparity in funding between African American/Black applicants and White applicants after accounting for observable factors. In response to this finding, Dr. Collins charged the Advisory Committee to the Director (ACD) to form a Working Group on Diversity in the Biomedical Research Workforce (WGDBRW).

The Working Group issued their report to the ACD on June 14, 2012. They provided thirteen recommendations for Dr. Collins’ consideration to increase the diversity of the biomedical research workforce as well as to mitigate the Ginther, *et al* findings. These recommendations were based on Working Group deliberations as well as extensive consultation with stakeholders, including a Request for Information and public meeting. The report is available at <http://acd.od.nih.gov/dbr.htm>.

After consulting with NIH senior leadership and discussing implementation options at the December 6, 2012 ACD meeting, Dr. Collins decided to implement a series of initiatives with the two main goals of increasing the diversity of the NIH-funded workforce. We have compelling evidence that this will help NIH accomplish our mission and ensure that all applicants are treated fairly in the peer review system. The initiatives include:

- A standing Advisory Committee to the NIH Director Working Group on Diversity to provide regular advice to the ACD and NIH Director on effective strategies to increase the representation of individuals from diverse backgrounds underrepresented nationally in biomedical research and to reduce disparities in research awards from applicants from backgrounds underrepresented nationally in biomedical research.
- The NIH Building Infrastructure Leading to Diversity (BUILD) program to increase enrollment of college graduates from diverse backgrounds underrepresented in biomedical research in graduate training. BUILD includes:
 - Rigorous mentored research experiences for 2 summers (while in college) and up to 2 years (post - graduation);
 - Tuition scholarships and stipends, for up to two years of undergraduate studies and additional loan repayment once in graduate school;
 - Salary offset and other infrastructure support for key faculty responsible for undergraduate research training;
 - Resources for highly effective mentors to train new mentors;
 - Support for an “innovation space” to enable organizations to develop novel approaches to increase the diversity of those entering PhD training;
- The National Research Mentoring Network (NRMN) of scientific leaders to enhance the retention and achievement of individuals from diverse backgrounds underrepresented in biomedical research. NRMN is designed to augment local mentoring efforts by connecting trainees and faculty to mentors from across the country and to provide relevant workshops in grantsmanship and career development.
- A single Coordination and Evaluation Center to link all BUILD programs and the NRMN.
- Activities to ensure the fairness of peer review, including:
 - Form expert, ad-hoc, subcommittee of ACD Working Group on Diversity to examine multiple hypotheses, including the role of unconscious bias, related to disparities in research awards;
 - Implement implicit bias and diversity awareness training for both the Scientific Review Officers (SRO) and members of review panels;
 - Pilot anonymizing of applications by removing identification of applicant and/or the applicant organization;
 - Enhance feedback to applicants that have Not Discussed applications;
 - Continue the Early Career Reviewer Program Pilot.
- Increased engagement by all NIH leadership through the appointment of a Chief Officer for Scientific Workforce Diversity to coordinate Agency initiatives to enhance diversity of research workforce, and the creation of Steering Committee Diversity Working Group as part of the NIH governance model.

Item

Mitochondrial Disease. - The Committee applauds the progress that NIH has made to advance research on mitochondrial disease and dysfunction. Among other activities, NICHD has worked to cultivate new researchers in the field and, in collaboration with ORDR and NINDS, continued support for the North American Mitochondrial Disease Consortium. ORDR also convened a major workshop with the participation of numerous ICs to identify scientific opportunities and barriers to research advances. The Committee requests that a strategy to implement the workshop recommendations be developed. (p. 104)

Action taken or to be taken

NINDS and NICHD support the North American Mitochondrial Disease Consortium, a multi-center collaboration and member of the NIH Rare Disease Clinical Research Network managed by ORDR. The consortium focuses on primary mitochondrial diseases and has developed a patient registry, a biorepository, and infrastructure for clinical research, including a natural history study and a phase I clinical trial. NINDS also supports and conducts additional studies on basic mitochondrial function in the brain and on neurodegeneration associated with primary mitochondrial diseases and mitochondrial dysfunction in other neurological conditions, as well as efforts to develop protective interventions.

In addition, the scientific conference titled “Translational Research in Primary Mitochondrial Diseases” was held in Rockville, MD, on March 8-9, 2012. Participants examined obstacles and opportunities in the research on primary mitochondrial diseases. The participants examined the opportunities for research collaboration as well as the use of new and emerging basic research and clinical technologies. The meeting concluded with a list of action items to be included in a white paper, which has since been developed. Recommendations included investments in basic biology and physiology of mitochondria; a stable long-term patient registry and biospecimen repository for the development of clinical trials; a partnership between NIH and patient support organizations and other interested parties to secure appropriate funding; a thoughtful and thorough development of research resources and methodologies; the development of a dedicated website for researchers; the establishment of a working group to determine overall goals and specific objectives to continue promising interactions; and to identify the mechanisms that provide the best opportunity for success. NIH will strive to address the workshop recommendations and resolve issues as they arise.

As a first step in addressing the workshop recommendations, NIH is organizing a working group to develop an implementation strategy to execute the strategic plan. The co-chairs have been identified and are currently finalizing the remaining membership.

Item

Mucopolysaccharidoses [MPS]. - The Committee encourages NINDS, NICHD, NIDDK, NIAMS, and ORDR to continue to expand research efforts in the development of effective treatments for MPS. The Committee also urges all relevant ICs and ORDR to continue funding research consortia and conferences on MPS and other lysosomal diseases, such as the annual Lysosomal Disease Network WORLD meeting and the Gordon research conference scheduled

for 2013. Finally, the Committee encourages NIAMS to continue to support investigator-initiated research focused on the skeletal complications associated with MPS. (p. 104)

Action taken or to be taken

NIH is committed to supporting the development of effective treatments for Mucopolysaccharidoses (MPS). NINDS, NIDDK, and the Office of Rare Diseases Research (ORDR) jointly support the Lysosomal Disease Network (LDN), one of 17 consortia within the Rare Diseases Clinical Research Network managed by ORDR. The LDN conducts studies specifically on MPS disorders, including two longitudinal studies in children with MPS disorders: one on brain structure and function, and another on bone disease and the effect of treatment with human growth hormone. People with MPS disorders have an increased risk of cardiovascular disease, and in a new pilot study, LDN researchers are also comparing carotid artery structure and function in people with or without MPS.

Beyond the Lysosomal Disease Network, NIH supports a range of additional studies to better understand MPS and related lysosomal storage disorders, and to develop new therapeutic approaches. While enzyme replacement can relieve some symptoms of these disorders, existing therapies do not cross the blood brain barrier and thus have limited effect on neurological complications. Through the NIH Small Business Innovation Research (SBIR) program, NINDS supports an effort to biologically re-engineer the deficient enzymes in MPS I and II for enzyme replacement therapy that can access the brain. Another small business seeks to devise the first small molecule drugs for treating MPS, and SBIR support for this work has facilitated a collaborative agreement with a large pharmaceutical company for further development. The same company has other SBIR support to develop biomarkers for diagnosing MPS and monitoring treatment responses. Investigator-initiated studies supported by NICHD and NINDS, as well as projects through the NINDS Cooperative Program in Translational Research, also focus on developing MPS treatments that effectively cross the blood-brain barrier, through small molecule, enzyme delivery, and gene and cell-based approaches. Further gene therapy and other treatment development efforts are supported by NIDDK, including a study with an emphasis on bone and joint disease in MPS, for which current therapies have similarly limited impact. NIAMS also funds a new clinician scientist studying bone disease and its treatment in children with MPS through a career development award. In association with the Lysosomal Disease Network, this scientist will also build a registry of patients with MPS that follows their growth and development, and characterizes their bone and endocrine disease features. Lastly, toward enabling early diagnosis and treatment before some devastating symptoms can occur, NICHD supports a number of grants and contracts to facilitate the addition of MPS and other lysosomal storage diseases to the recommended uniform newborn screening panel.

NIH continues to support scientific conferences that bring together researchers with an interest in MPS and other storage disorders. NINDS and ORDR also supported the 2011 Lysosomal Disease Gordon Research Conference. In addition, NICHD, NINDS, and NIDDK supported the 8th Annual Lysosomal Disease Network's WORLD ("We're Organizing Research for Lysosomal Diseases") Symposium in February, 2012, and NINDS and NIDDK are supporting the 9th WORLD Symposium in 2013. This is the one of the preeminent forums for researchers to share their work on the diagnosis, management, and treatment of lysosomal storage disorders, including MPS.

Item

National Children's Study. - The Committee is troubled that after appropriating nearly \$1,000,000,000 for the NCS since the first work on it began in fiscal year 2000, only a few thousand children have been enrolled and fundamental questions about the project's implementation still remain, particularly regarding the methods that will be used to recruit participants. The Committee hopes that the budget request, a 15-percent reduction below the fiscal year 2012 level, represents a positive sign that NIH intends to bring the costs of the NCS under control and spend its appropriation more efficiently. NIH's recently announced plan to switch to a provider-based rather than a household-based recruitment strategy will help achieve some of the necessary savings and may offer scientific benefits as well. At the same time, special efforts must be made to ensure that the new strategy will not leave out disadvantaged or underrepresented groups that are most negatively affected by health disparities. Plans to collect environmental as well as biological samples also should not be sacrificed. Most important, it remains unclear whether a provider-based approach can accommodate the original goal of constructing a national probability sample that could be generalized to the entire U.S. population. The Committee believes NIH should make every possible effort to fulfill that goal within a sustainable long-term budget. The Committee directs the Secretary to enter into an agreement within 90 days of enactment of this act with the National Academy of Sciences to review the NCS' sampling strategy. The Committee is also aware of the confusion and disruption caused by NIH's decision to let the Vanguard Study contracts expire—a decision that caught many academic institutions by surprise. The Committee strongly urges NIH to improve its level of communication with the research community about any future changes to the project. (p. 105)

Action taken or to be taken

The overall goal of the National Children's Study (NCS) remains the same as it has been since the Congress authorized the Study in 2000 – to improve the health and well-being of children and to identify the antecedents of healthy adulthood by examining the multiple effects of environmental influences and biological factors on the health and development of children from birth or before, and following them until age 21. NCS has several components, including a pilot or Vanguard Study, a Main Study to collect exposure and outcome data, and formative research.

The sample frame for the NCS Vanguard and Main Studies was initially based on a national probability sample using geography and selecting about 100 of the approximately 3,000 counties in the United States. The initial recruitment technique within the selected geographic areas was household contact by NCS staff going door-to-door. The Vanguard Study was launched in January 2009 and, by summer 2009, field experience suggested that the household contact recruitment strategy had scientific limitations and was not feasible with available resources. Thus, in 2010, three new recruitment strategies were launched to evaluate other options for recruitment. By late 2011, NCS had sufficient data on the scientific validity, cost, and logistical feasibility of these strategies, which were discussed with the NCS Federal Advisory Committee and the NIH leadership.

NCS leadership now proposes that the Main Study sampling frame be based on provider location, using providers associated with hospitals and birthing centers in selected geographic

areas. The study still aims to recruit 100,000 participants, but with several components: a national probability birth cohort at hospitals and birthing centers (because almost all births occur in these facilities), a broad-based prenatal cohort, a smaller preconception cohort, and targeted supplemental recruitment for underrepresented populations. NIH contracted with the National Academy of Sciences for an evaluation workshop to review the proposed design of the Main Study. The workshop took place on January 11, 2013. NCS leadership will use the results of this workshop, advisory board meetings, a request for information that was published in the Federal Register in February, and the results of field work designed to test the logistics of the proposed method to determine a final plan.

The overall emphasis continues to be on capturing a wide range of environmental exposures. Understanding environmental exposures in the prenatal period also remains a core focus of the NCS, and will be achieved by collecting biospecimens from pregnant women and data and environmental samples from their homes. The environmental samples are especially important because they are not routinely collected by health care providers. The NCS biobank repository for human biological specimens and environmental samples already has collected about 125,000 specimens from pregnant women and their homes and, to date, has distributed thousands of specimens for analysis and additional scientific projects.

The nearly 4,000 children already recruited into the NCS Vanguard Study will continue to be followed by a NCS contractor until they are aged 21 years. In September 2012, four new awards were made to carry out the NCS Vanguard 2.0 Study, which will continue to test future Main Study protocols three to four years in advance of the Main Study. A NCS Vanguard Study Regional Operations Center Network will be established, consisting of four regional divisions of 10 current Study Locations each, based on geography (Central, East, South, and West Regions). Each region has a separate contract. The Vanguard 2.0 Study will implement the next phase of the NCS Vanguard Study with a focus on the activities of data collection and evaluation, participant retention, and study visit development and assessment.

NCS has expanded its regular communications with the research community and other stakeholders in the study. Updates on new developments are provided regularly during the NCS Federal Advisory Committee meetings, weekly Vanguard Center conference calls with the Program Office, and multiple meetings with stakeholders.

In addition to mandating the study, the Children's Health Act of 2000 directed NICHD to lead a consortium of federal agencies to plan and implement the study. The NCS program office has revitalized a broad Federal Consortium of agencies interested in the study, discussing the sampling design at the Consortium's August 2012 meeting. NCS also funded a workshop in February 2013 for potential users of the data that will be produced by the study, which drew participation from a broad cross-section of researchers.

Item

National Primate Research Centers. - The Committee supports the NPRCs and expects they will receive the same level of attention in the OD that they received in the now-dissolved National Center for Research Resources. (p. 105)

Action taken or to be taken

The Office of Research Infrastructure Programs (ORIP) in the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), part of the NIH Office of the Director (OD), currently supports the National Primate Research Centers (NPRCs). The funding levels and type of programmatic, review, grants management and other administrative support did not change when the NPRC program was transferred to the OD. As in the past under the former National Center for Research Resources (NCRR), the NPRC program continues to be administered by the Division of Comparative Medicine, the entity within DPCPSI with authority to fund and oversee the centers. In addition, all NPRC-related programs, including the NPRC consortium, are administered by the same federal scientific program staff.

Item

Neurofibromatosis [NF]. - The Committee continues to support efforts to increase funding and resources for NF research and treatment at multiple NIH Institutes, including NCI, NHLBI, NINDS, NICHD, NIMH, NIDCD, NIAMS, NEI, and NHGRI. The Committee requests brief updates on NF-related activities at these ICs in the fiscal year 2014 congressional budget justification. (p. 105)

Action taken or to be taken

The neurofibromatoses (types 1 and 2, or NF1 and NF2, and schwannomatosis) are autosomal dominant genetic disorders in which nerve tissue grows tumors (i.e., neurofibromas) that may be benign or may cause serious damage by compressing nerves and other tissues. The NIH Institutes and Centers (IC) work both collaboratively and in a mission specific manner to make advances in NF research and treatment. For instance, the Trans-NIH NF Working Group, spearheaded by NINDS, holds biennial meetings to coordinate NF research across ICs. The most recent meeting of the Trans-NIH NF Working Group was in February 2012 and included representatives from eight ICs, the Department of Defense, and advocacy groups. NINDS-supported researchers are investigating the mechanisms underlying the development of tumors in NF, and developing therapeutics to prevent NF tumors. NINDS also funds studies to understand how mutations in the genes for NF alter brain development and the function of neurons, which may contribute to learning, cognitive, and neurological impairments.

NCI supports a comprehensive research program directed at neurofibromatosis (NF) and its related cancers, including investigation of the biology of the Neurofibromatosis type 1 (NF1) and/or Neurofibromatosis type 2 (NF2) tumor suppressor genes and their protein products, and the consequences of their deactivation that underlie NF and cancer. NCI also funds work focused on the identification of rare and under-recognized cancers that may be associated with NF1, including development of a clinical setting specifically to evaluate these patients. NCI has taken a leadership role in the Department of Defense sponsored NF Consortium to accelerate the development and conduct of clinical trials in NF, and NCI has established one of the largest clinical trials programs for children and young adults with NF1.

The first genome-wide association study (GWAS) to identify susceptibility genes in NF1 was conducted at NCI, and the follow-up fine-mapping and replication efforts are currently under way. NCI is also applying recent advances in sequencing technologies to sequence NF1-

associated tumors. In the past year, NCI investigators have made progress in identifying genes contributing to development of NF-associated astrocytomas, peripheral nerve sheath tumors, pheochromocytomas and gliomas.

Through its Intellectual and Developmental Disabilities Research Center at the University of Alabama-Birmingham, NICHD is supporting and participating in the DOD-sponsored Neurofibromatosis Consortium. Among other activities, the Consortium is conducting clinical trials on treatments for some of the tumors caused by NF1, and on the use of pharmaceuticals to improve cognitive outcomes in children with NF1 who have learning disabilities. NICHD investigators are studying the prevalence of endocrinopathies in children with NF1. Specifically, they aim to determine how bone mineral density and vitamin D absorption are affected in children with NF1. Scientists also are evaluating the relationship between pubertal development and growth of benign fibrous tumors (neurofibromas), and investigating the endocrine-related side effects of new chemotherapeutic drugs that could be used to treat those tumors.

NHLBI-supported investigators recently reported evidence of a new role for the NF1 gene that causes the disease in mice. Mice with a mutation in NF1 showed abnormal development of the heart's epicardium, or surface layer, which led to an increase in a type of cell known to cause fibrosis. The investigators also identified a protein that partially reversed the effect.

NIMH supports an exploratory intervention trial in children with NF1. Preclinical studies supported by NIMH have shown that mutations in the gene NF1 leads to learning deficits that can be attenuated with lovastatin (a cholesterol-lowering class of drug). Building on this research, NIMH is now conducting a clinical 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).

NF2 occurs in about one out of every 40,000 Americans. NF2 is typically characterized by bilateral vestibular schwannomas (benign nerve tumors) that grow specifically in the auditory-vestibular nerve that travels from the ear to the brain and can cause hearing and balance disorders. NIDCD supports research exploring how proteins involved with the NF2 mutation may be used to test and develop molecular and drug therapies for NF2 disorders, and to develop auditory prostheses for brainstem and midbrain for individuals who have lost that nerve function from NF2 tumor surgical removal. In addition, NIDCD investigators are participating in a clinical research study and a prospective study to further our understanding of the most appropriate therapy and the optimal timing of intervention. NIDCD and NCI are collaborating on a natural history study and longitudinal assessment of people with NF1, examining the auditory characteristics across individuals. In addition, NIDCD, NINDS, and NCI intramural and extramural scientists, scientists are examining the effect of bevacizumab, a potential therapeutic biologic agent, on both auditory and vestibular function as well as its tumor responses.

NF is also an important model through which to study the genomics of cancer predisposition, and NHGRI continues to develop plans for a research portfolio over the next three to five years that will include considerations of diseases such as NF.

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, interstitial cystitis, irritable bowel syndrome, chronic headache, temporomandibular disorders, and vulvodynia. 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 and mechanistic pathways of these overlapping conditions, with a state of the science meeting scheduled for summer 2012. The Committee hopes that the meeting will lay out a clear and concrete set of recommendations for an aggressive trans-NIH research agenda. The Committee notes that the chronic pain conditions listed above are also ideal candidates for inclusion in the Patient-Reported Outcomes Measurement Information System, as many chronic pain patients use multiple individualized approaches to manage pain symptoms. (p. 105-106)

Action taken or to be taken

NIH recognizes the opportunity for improved mechanistic understanding of why certain chronic pain conditions frequently co-occur. Recent research results of a study funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) found that chronic pain conditions such as vulvodynia, fibromyalgia, and others often may be underdiagnosed, and that certain patterns emerge among women suffering from these conditions, such as increased systemic sensitivity to pain.

NIH organized several workshops and meetings in 2011, including the 2011 NIH Pain Consortium Symposium on the mechanisms and management of overlapping chronic pain conditions. As a result of these workshops, as well as meetings with the Chronic Pain Research Alliance, a new trans-NIH Overlapping Chronic Pain Conditions Working Group was formed in fall 2011. This working group, in partnership with academic and advocacy communities, held a two-day workshop on overlapping chronic pain conditions on August 13-14, 2012 on the NIH Campus. The workshop focused on our current understanding of these disorders with the goal of developing a coordinated research strategy addressing the causes, risk factors, mechanisms, outcome measures, and diagnoses of these overlapping conditions. A number of potential research gaps and areas of scientific opportunity were presented and discussed, and NIH, with input from the trans-NIH Overlapping Chronic Pain Conditions Working Group, is currently considering the recommendations that emerged from this meeting.

NIH also continues to support other research activities targeting specific conditions mentioned by the Committee. The Office of Research on Women's Health (ORWH) along with NIH institute partners, has provided long-term, consistent support for research on many overlapping chronic pain conditions, including chronic fatigue syndrome. ORWH leads the Trans NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Working Group, and co-sponsors funding opportunity announcements focused on the etiological and mechanistic aspects of ME/CFS together with other NIH Institutes and Centers. In April 2012, NIH released its *Research Plan on Vulvodynia*, building upon input received from a broad array of scientists,

health care professionals, and patients. The plan lays out an agenda for rigorous scientific research to answer questions and fill in knowledge gaps about vulvodynia. The National Institute of Neurological Disorders and Stroke (NINDS) supports a large-scale study to identify risk factors and underlying physiological mechanisms of five chronic pain conditions that frequently co-occur (fibromyalgia, episodic migraine, vulvar vestibulitis, irritable bowel syndrome, and temporomandibular joint disorders).

A major challenge in the diagnosis and management of chronic pain conditions is the difficulty in accurately and precisely tracking symptoms that are not amenable to clinical measures such as lab tests. In 2004, the NIH Common Fund launched the Patient-Reported Outcomes Measurement Information System (PROMIS; <http://commonfund.nih.gov/promis/>), an effort to enhance the precision of measures of patient-reported symptoms or outcomes. This system is applicable to a wide range of disorders, including chronic pain conditions, and can be used to strengthen clinical research studies and/or design new treatment plans to improve the management of chronic disease. PROMIS measures have been standardized, so there are common metrics across conditions, allowing for comparisons across a variety of diseases and individualized treatment plans. PROMIS measures relevant to pain include measures for pain behaviors, pain interference in aspects of life, pain intensity, and physical function capability.

Item

Pain. - The Committee commends NIH for its efforts so far to respond to the IOM report “Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research.” For example, NIH has designated NINDS as the lead Institute for coordinating pain research efforts across the organization; selected a cadre of 11 Centers of Excellence for Pain Education; begun to develop new informational material for the public and medical professionals on pain conditions; and instituted more frequent meetings of the NIH Pain Consortium. The Committee strongly urges NIH to expand on such efforts while giving appropriate attention to overlapping chronic pain conditions that solely or disproportionately impact women. The Committee believes that pain research would be an appropriate subject for inclusion in the Common Fund, as advances in this area would benefit all Institutes. Finally, the Committee agrees with the IOM report recommendation that NIH increase financial resources and staffing support for the Pain Consortium. (p. 106)

Action taken or to be taken

The IOM report “Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research” emphasized the urgency to address the high burden of pain, and as the Committee notes, NIH has been working to address many of the report’s recommendations. NINDS leads NIH’s pain research efforts and provides support to the NIH Pain Consortium and the Interagency Pain Research Coordinating Committee (IPRCC). The NINDS director, Dr. Story Landis, serves as chair of both the IPRCC and the NIH Pain Consortium Executive Committee, and in those roles leads enhanced coordination of pain research at NIH and helps strengthen coordination across agencies. In addition, NINDS recently appointed a Health Science Policy Advisor dedicated to staffing and supporting the activities of the NIH Pain Consortium and the IPRCC.

NIH has been moving forward with other recommendations from the report, including: improving the process for developing new agents for pain control; coordinating a portfolio analysis through the IPRCC to inform strategies for increasing support for interdisciplinary pain research; increasing the conduct of longitudinal research in pain; and enhancing and increasing training opportunities for pain researchers, including funding Centers of Excellence in Pain Education.

NIH recognizes the disproportionate burden of many chronic pain disorders on women. To begin to address these issues, NIH organized several workshops focused on pain in women, including the 2011 NIH Pain Consortium Symposium on the mechanisms and management of overlapping chronic pain conditions. In Fall 2011, NIH formed the trans-NIH Overlapping Chronic Pain Conditions Working Group to help coordinate and advance these areas of research. This working group held a workshop on August 13-14, 2012 on the NIH Campus. The workshop focused on current understanding of chronic overlapping pain disorders with the goal of developing a coordinated research strategy addressing the causes, risk factors, mechanisms, outcome measures and diagnoses of these conditions. A number of potential research gaps and areas of scientific opportunity were presented and discussed. NIH is considering the recommendations that emerged from this workshop.

The NIH Office of Research on Women's Health (ORWH) convened a scientific meeting on chronic pain syndromes as part of its strategic planning process. Research priorities were developed and are guiding next steps related to the study of pain, with a focus on many of the diseases associated with pain in women. The National Center for Complementary and Alternative Medicine (NCCAM) recently announced the appointment of a world-renowned pain researcher to lead a new multidisciplinary pain program as part of the NIH Intramural program. This new research program focuses on the role of the brain in perceiving, modifying, and managing pain and it will complement basic science and clinical research efforts of other ongoing intramural research programs.

The NIH Common Fund supports programs that are expected to have a transformative impact on a trans-NIH area of science within a 5-10 year period. Science covered by these programs must have both significant challenges and significant opportunities. The Common Fund's Office of Strategic Coordination and the NIH Pain Consortium are working together to identify opportunities in pain research that are ripe for Common Fund investment.

Item

Pediatric Low Grade Astrocytoma [PLGA]. - The Committee is encouraged by advancements in research on slow-growing children's brain tumors but remains concerned by the long-term physical and cognitive disabilities caused by surgery, chemotherapy, and radiation treatments for PLGA children. The Committee urges NIH to establish a special emphasis panel with a focus on identifying and validating new therapeutic targets in these tumors. Research should emphasize the development of novel preclinical models of pediatric brain tumors (both mouse and other nonmammalian models), novel drug development and testing, target identification and validation, and improved drug delivery modalities. The Committee requests an update on these topics in the fiscal year 2014 congressional budget justification. (p. 106)

Action taken or to be taken

NCI continues to support research that builds upon advances in understanding the biology of Pediatric Low Grade Astrocytoma (PLGA), particularly the identification of genomic alterations involving the BRAF gene in the vast majority of pediatric pilocytic astrocytomas (the most common PLGA). The BRAF mutations are of two primary types: one type is identical to the BRAF mutation (BRAF V600E) that occurs in a high percentage of patients with the skin cancer melanoma, while the other type of alteration appears to be unique to pilocytic astrocytomas. NCI-supported investigators and other research teams have shown that additional types of PLGA (e.g., ganglioglioma and pleomorphic xanthoastrocytoma) have the same BRAF V600E mutation. These new understandings provide important opportunities for clinical translation to develop new therapeutic options for children with PLGA.

Additionally, NCI-supported research has identified the relationship between a set of recurring genomic alterations (including BRAF rearrangements, BRAF V600E, and others) in a large cohort of pediatric low-grade gliomas. Future advances in understanding the genomic alterations of PLGAs are anticipated, as genome sequencing of pilocytic astrocytomas is being undertaken by a team of German pediatric brain tumor researchers through the International Cancer Genome Consortium (ICGC), of which NCI is a partner and funder of related work within the ICGC.

Preclinical models for PLGA are also being developed that will allow research teams to identify promising candidate treatments for this disease. This includes research by the NCI-supported Pediatric Preclinical Testing Program, which led to a Phase I Pediatric Brain Tumor Consortium clinical trial of selumetinib in children with pilocytic astrocytoma, also supported by NCI. Selumetinib is a targeted agent that inhibits the MEK pathway, which is involved in cancer cell proliferation and survival. The Phase I trial clinical protocol was modified in August 2012 to include a broader range of pediatric patients with PLGA, and it should complete accrual in 2013. A mouse model of astrocytoma/glioblastoma developed by intramural NCI investigators has been utilized to address a number of key research questions and challenges, including the identification of a chromosomal target that affects the formation of astrocytomas in the spine and another that relates to gender differences in susceptibility to PLGA. The mouse model has also been used to screen potential drugs for both high- and low-grade astrocytomas, which may lead to finding drugs with lower toxicity in children.

Intramural NCI investigators, in partnership with the Pediatric Brain Tumor Consortium, led a nationwide trial of an anticancer drug called lenalidomide in children with brain tumors. Results showed clinical responses and prolonged stable disease. The drug was well tolerated at doses higher than those used in adults, suggesting that children may be well suited to therapy with this agent. NCI intramural investigators, in collaboration with NCI-supported extramural partners in the Children's Oncology Group, are now leading a Phase II combination trial of lenalidomide with radiation therapy for PLGA that initiated enrollment in March 2012.

Item

Pregnancy Health Status. - Epidemiologic studies have shown that a woman's health status during pregnancy is associated with her health after pregnancy, suggesting that findings in pregnancy may be a better indicator for determining a woman's future health status than traditional risk factors. The Committee encourages NICHD, NHLBI, and NIDDK to work together to more closely study these epidemiologic findings in an effort to identify predictive markers during pregnancy for subsequent heart disease and diabetes; develop tests to evaluate health after pregnancy; and test interventions both during and after pregnancy that may mitigate risk. (p. 106)

Action taken or to be taken

NIH agrees that pregnancy is a "stress test" for long term health, potentially unmasking future maternal health complications. More than half of U.S. women of childbearing age are now considered overweight or obese, with prevalence rates being higher among some racial/ethnic minority populations and those of low socioeconomic status. In addition, amounts of gestational weight gain (GWG) and post-partum weight retention have been increasing over time, resulting in higher pre-pregnancy body mass index (BMI) during subsequent pregnancies. Numerous studies have linked overweight, obesity, and/or excessive GWG during pregnancy to adverse health consequences in both mothers and offspring. Short-term adverse outcomes include maternal and fetal mortality, pregnancy-induced hypertensive disorders, gestational diabetes mellitus, caesarean delivery, abnormally large fetuses, and congenital abnormalities. Longer-term adverse outcomes include obesity and related metabolic conditions, such as type 2 diabetes, in both the mother and their offspring. This vicious cycle of obesity and metabolic disorders in the offspring of obese women poses a serious public health concern. The goal of research on interventions during pregnancy is to identify the means to ameliorate inappropriate gestational weight gain and/or influence metabolic status of the mother, in order to reduce 1) post-partum weight retention, 2) the incidence of gestational diabetes and subsequent development of type 2 diabetes in the mother, and 3) the risk for obesity, metabolic disorders, and adverse cardiovascular outcomes in both the mother and her offspring.

NICHD has partnered with NHLBI and other NIH Institutes and Centers (NIDDK, NCCAM, ORWH, OBSSR) to study the effects of lifestyle interventions during pregnancy on short- and longer-term outcomes in mothers and children. In 2009, NICHD joined NHLBI in funding the Early Adult Reduction of weight through Lifestyle Interventions (EARLY) trials to test an electronically-delivered pre-delivery and postpartum lifestyle intervention to ascertain its effect on weight gain during pregnancy and postpartum weight retention. Enrollment is complete and intervention delivery and follow-up are ongoing. In 2011, NICHD partnered with NIDDK, NHLBI, and other NIH offices to support a consortium of seven clinical trials testing unique lifestyle interventions designed to promote appropriate gestational weight gain, decrease postpartum weight retention, and improve body composition and metabolic status among both mothers and offspring. This consortium, Lifestyle Interventions For Expectant Moms (LIFE-Moms), is set to begin recruitment in October, 2012.

The Diabetes Prevention Program sponsored by NIDDK demonstrated that women with a history of gestational diabetes could reduce their risk for developing diabetes later in life with lifestyle changes or diabetes medication; the study continues to assess long-term effects of the trial

interventions on this group of women a decade later. NICHD is continuing long-term assessment of women and their children who participated in a clinical trial of the longer term effects of mild gestational diabetes (GDM) during pregnancy, to evaluate metabolic dysfunction in children aged 5-9 years of women who received treatment for mild GDM compared with those children born to women who did not receive treatment.

Current medical practice is based on the assumption that women return to normal health following a pregnancy complicated by preeclampsia or other adverse pregnancy outcomes. Recent findings, primarily based on retrospective studies, highlight the opportunity for prospective research to systematically elucidate the aspects of cardiovascular risk associated with preeclampsia. The Office of Research on Women's Health supports the Advancing Novel Science in Women's Health Research Program in collaboration with other NIH Institutes and Centers. This program addresses, among other studies, novel therapeutic approaches for the treatment of preeclampsia. NICHD joined with NHLBI to issue a new funding opportunity announcement in August 2012, "Pregnancy as a Window to Future Cardiovascular Health: Adverse Pregnancy Outcomes as Predictors of Increased Risk Factors for Cardiovascular Disease." The new solicitation, which leverages the existing *Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be* cohort funded by NICHD, is intended to support cardiovascular risk assessment at approximately two years postpartum in women with and without complications (e.g. preterm birth, preeclampsia, fetal growth restriction) during their first pregnancies.

Item

Rehabilitation Research. - The Committee recognizes and supports efforts of the Blue Ribbon Panel on Medical Rehabilitation Research to identify gaps in rehabilitation research. The Committee believes that the panel's findings warrant meaningful steps by the Director to enhance the stature of, and emphasis is on, medical rehabilitation and disability research at NIH. (p. 106)

Action taken or to be taken

In 2011, NIH leadership appointed a Blue Ribbon Panel on Medical Rehabilitation Research. Since its initial meeting in October 2011, the Panel completed an assessment of rehabilitation research across NIH and finalized recommendations to NICHD. In 2012 the panel conducted a survey of selected Institutes and Centers about their rehabilitation research portfolios, interviewed representatives from various coordinating bodies across NIH about their respective activities, and gave public presentations of the Panel's findings to the National Advisory Child Health and Human Development Council and the National Advisory Board on Medical Rehabilitation Research.

The Panel considered six issues in the assessment: 1) a definition of rehabilitation research, 2) the scope of rehabilitation research within NIH, 3) the activities and effectiveness of the National Center for Medical Rehabilitation Research (NCMRR), housed within the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), 4) the usefulness and feasibility of coordination of all rehabilitation research within NIH, 5) the scientific

opportunities in the field of rehabilitation research today, and 6) the barriers that prevent rehabilitation science from progressing.

The Panel commended NCMRR for its accomplishments given existing resources, but argued that in order to thrive, rehabilitation research at NIH requires increased funding and coordination. The Panel recommended that NIH create a new office within the NIH Office of the Director, to support rehabilitation research. The Panel recommended that this entity be provided dedicated funding and granting authority and that it should play a central role in coordinating rehabilitation research within NIH and with other federal agencies. Another recommendation concerns a transdisciplinary strategic plan at NIH – updated periodically and developed in collaboration with advocates, researchers, clinicians, and persons with disabilities – to address rehabilitation problems across the lifespan and myriad conditions.

In evaluating NIH’s existing research portfolio, the Panel identified several gaps. The Panel urged NIH to expand research across the spectrum of translational research, to fund larger-scale clinical trials and comparative and cost-effectiveness studies; to support more research on patient activity and societal participation (beyond basic pathophysiology and physical impairments); to achieve a better balance between research on biological mechanisms (currently the majority of research represented in the NIH portfolio) and on interventions; and to address the full spectrum of diseases and disorders relevant to rehabilitation. However, given the high prevalence of disability in the U.S. and the scientific opportunities across all areas of rehabilitation research, the Panel also contended that a substantial increase in funding across all areas of rehabilitation research is warranted.

NIH leadership expressed appreciation to the Panel for the time and energy that members dedicated to their task and the thoroughness of their recommendations. NICHD is meeting with the leadership of several other Institutes and Centers to discuss the Panel’s findings and determine the next steps for addressing the recommendations.

Item

Sex-Based Biology. - It is now more than 10 years since the IOM report “Exploring the Biological Contributions to Human Health: Does Sex Matter?” confirmed that biological differences between males and females affect health, burden of disease, healthcare, and health outcomes, but significant disparities continue to exist. Understanding the basic biology of the impact of sex/gender in development, diagnosis, and treatment of disease could help improve the health of women. Therefore, the Committee urges NIH to analyze sex at all levels of biomedical research, including the basic animal and cellular levels, and to form interdisciplinary teams of basic and clinical investigators interested in unraveling the biology of sex differences. (p. 107)

Action taken or to be taken

The Office of Research on Women’s Health (ORWH) and the NIH Institutes and Centers (IC) continue to support and expand activities through partnerships across NIH, emphasizing analysis and publication of data by sex across the spectrum of biomedical research. In 2010, the NIH Strategic Plan for Women’s Health Research and Sex differences was updated. One major goal

of the new strategic plan is to increase the study of sex and gender differences in basic biomedical and behavioral research.

In response to a 2011 IOM report on the progress of women's health research, ORWH funded an IOM workshop targeted to journal editors and publishers about the added value of the publication of analyses by sex in the scientific literature. The 2012 summary report provides suggestions for strategies to increase sex-specific reporting of scientific data.

<http://www.iom.edu/Activities/Women/SexSpecificReporting.aspx>

In 2001, ORWH announced the Specialized Centers of Research (SCOR) on Sex and Gender Factors that Affect Women's Health. This program was designed to attract and support teams of investigators to conduct interdisciplinary research on the role of sex and gender factors in health or disease. After a decade, the investigators are serving as a model for interdisciplinary sex differences research. In FY 2011, ORWH and co-sponsoring NIH ICs and the Food and Drug Administration (FDA), re-issued the ORWH developed SCOR program under the name *Specialized Centers of Research (SCOR) on Sex Differences*. Eleven awards were made in August 2012. <http://orwh.od.nih.gov/interdisciplinary/scor/index.asp>

Select examples of SCOR funded research include:

- The National Institute on Diabetes, Digestive and Kidney Diseases (NIDDK) is co-supporting, with ORWH, two SCORs that are exploring the biology underlying sex differences in susceptibility to and treatment of urinary tract infections caused by *E.Coli* and susceptibility to two pain conditions that are more prevalent in women, irritable bowel syndrome and interstitial cystitis/painful bladder syndrome.
- Three newly awarded SCORs, funded by the National Institute of Drug Abuse (NIDA) and ORWH will conduct sex differences research related to nicotine and cocaine addiction, including preclinical and brain imaging studies.

Item

Sleep Disorders. - The Committee recognizes that sleep or circadian disorders impact conditions such as hypertension, diabetes, obesity, heart attack, and stroke. The Committee urges implementation of the National Sleep Disorders Research Plan's recommendations for the continuation of multi-Institute research collaborations to address such conditions. (p. 107)

Action taken or to be taken

The National Center on Sleep Disorders Research (NCSDR), a component of NHLBI, is the principal point of coordination for NIH sleep and circadian research. At a public meeting of the Sleep Disorders Research Advisory Board held in fiscal year 2012, NCSDR outlined an agenda for implementing the NIH Sleep Disorders Research Plan, reviewed ongoing sleep initiatives, and obtained community input on current and planned activities. Early in FY 2013, a public meeting of the Sleep Disorders Research Advisory Board was convened and monthly meetings of the trans-NIH Sleep Research Coordinating Committee were held to assess progress on the NIH Sleep Research Plan and facilitate NIH-wide scientific collaborations.

Examples of current multi-Institute collaborations include the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (NuMoM2B), an NICHD project for which NHLBI supports collection of data on sleep-disordered breathing in pregnancy to determine whether the abnormality increases risk of developing hypertension, diabetes, or preeclampsia during pregnancy or experiencing delivery complications. A new NHLBI–NICHD initiative, in FY 2013, will obtain follow-up data on the NuMoM2B cohort to assess the influence of sleep apnea during pregnancy on maternal and infant cardiovascular health two years postpartum. NHLBI, NICHD, and NINR are partners on an initiative to stimulate basic research on the etiology and pathophysiology of sleep apnea in pregnancy. An ongoing NHLBI–NIDDK partnership leverages a study of obese patients with diabetes to determine whether sleep apnea increases the severity of diabetes or reduces the effectiveness of physician-recommended treatments for weight loss and exercise.

Support for the collection of national data on sleep disorders in CDC surveillance studies is coordinated by NHLBI with other participating NIH components. As a result of a NHLBI–NCI collaboration, new technology is being used in fiscal year 2012 to obtain for the very first time nationally representative estimates of both sleep and physical activity in relation to risk of disease and quality of life.

Item

Tox21 Program. - The Committee supports NIH’s leadership role in the Tox21 program, a collaborative effort with the EPA and the FDA to adopt advanced molecular biological and computational methods in lieu of animal toxicity tests for conducting chemical risk assessments. The Committee encourages NIH to continue to expand its extramural support for the use of human biology-based experimental and computational approaches in health research to further define toxicity and disease pathways and develop tools for their integration into evaluation strategies. Extramural and intramural funding should be made available for the evaluation of the relevance and reliability of Tox21 methods and prediction tools to assure readiness and utility for regulatory purposes, including pilot studies of pathway-based risk assessments. The Committee asks NIH to provide a report on fiscal year 2012 and 2013 funding for these activities in the fiscal year 2014 congressional budget justification. (p. 107)

Action taken or to be taken

As noted by the Committee, the purpose of the Tox21 program is to characterize toxicity and disease pathways and to use that information to develop better tools for human health hazard identification. The specific research now under way attempts to link chemical exposures to specific changes in the expression of genes in cells or tissues, link these gene expression changes to molecular pathways recognized to be activated in response to toxicants, and study the similarity of these patterns to pathway changes involved in disease processes. To achieve this, NIEHS, in collaboration with EPA’s National Center for Computational Toxicology (NCCT), NCATS’s NIH Chemical Genomics Center (NCGC), and FDA, is supporting multiple avenues of research and development.

In FY 2012, the Tox21 community:

- Continued the optimization of novel biological target screens for use in high throughput *in vitro* screening.
- Screened 12,174 substances in 65 quantitative high throughput screening (qHTS) assays and ~1400 substances in 39 qHTS assays as part of the assay validation process prior to screening the complete library, generating 1.4 million concentration response curves.
- Supported the screening of 50 compounds in ~600 mid-throughput assays as part of the EPA's ToxCast Program.
- Evaluated the applicability of different dose response models to qHTS data.
- Integrated human adverse health data into Tox21.
- Supported the development of several new gene expression platforms using cells capable of metabolizing environmental chemicals as well as commercially available human stem cells.
- Linked chemically-induced rodent gene expression patterns with approximately 50 end points typically seen in animal toxicology experiments.
- Developed methods for screening preserved paraffin tissue blocks from hundreds of older rodent toxicity studies performed by NTP to identify gene expression patterns; NTP tissue archives contain 5 million paraffin tissue blocks, which can be studied for pathways associated with disease.

For FY 2013, Tox21 will continue work on these projects and will begin the evaluation of 1,090 human cell lines representing nine racial groups, for differential toxicity to a variety of model toxicants. Utilization of these *in vitro* approaches to understand genetic differences may explain inter-individual variability in susceptibility to toxicant induced disease and dysfunction.

The results from these and other ongoing studies will aid in the validation and use of Tox21 approaches to improve hazard identification, characterization, and risk assessment.

NIH funding for FY 2012 was \$5.5 million, FY 2013 is approximately \$4.0 million, and FY 2014 is approximately \$5.0 million.

Item

Tuberous Sclerosis Complex [TSC]. - The Committee understands that TSC is the largest single genetic cause of more prevalent neurological disorders such as autism and epilepsy and therefore encourages NINDS to focus resources on new drug targets for TSC and encourages NINDS and NIMH to focus resources on clinical trials for TSC. Because TSC impacts tumor growth and health of multiple organ systems, including skin, lung, kidney, and brain, the Committee encourages NCI, NIAMS, NHLBI, NIDDK, NINDS, NICHD, and ORDR to focus resources on methods to detect and treat manifestations of TSC in these organ systems. (p. 107)

Action taken or to be taken

Tuberous Sclerosis Complex (TSC) research is a high-priority trans-NIH effort. The genes affected in TSC (TSC1 and TSC2) encode proteins within the mTOR signaling pathway, which regulates cell growth and protein production in various cell types in the body. A better understanding of the mTOR pathway will provide insights into how mutations in TSC1 and

TSC2 lead to abnormalities in multiple organ systems, and could lead to the development of drugs to treat the various manifestations of TSC.

NINDS, NIMH, and NICHD fund research investigating the role of TSC1 and TSC2 genes and their related pathways in brain development and neural signaling, including studies on the development of epilepsy and autism as well as altered sleep regulation and circadian rhythms. For example, NINDS and NICHD are co-funding an Autism Center of Excellence Network that will monitor brain development in infants with TSC to better understand the development of autism in the subset of children affected with this condition. As part of the NINDS Epilepsy Centers without Walls program, NINDS is providing planning support toward establishing a collaborative research center that would focus on preventing the development of epilepsy, or epileptogenesis, in people with TSC. With this initial funding, investigators will work to develop optimal parameters and necessary infrastructure for potential antiepileptogenic drug trials in TSC. Other NINDS-funded researchers are developing advanced neuroimaging techniques to improve localization of epileptogenic brain regions for surgical resection in people with TSC. In addition to research focused directly on TSC, studies of non-TSC forms of autism and epilepsy may lead to insights and advances for TSC. For example, NIMH research is developing better ways to image the brain of children with ASD and other neurodevelopmental disorders, which will enable dramatic improvements in our capacity to chart the natural history of these disorders over the lifespan.

In addition to the brain, TSC affects a number of other organ systems. Multiple Institutes, including NIAMS, NCI, NHLBI, and NIDDK, are funding research on signaling in the mTOR pathway and its involvement in both normal cellular processes and abnormal conditions and diseases. As commonalities between the molecular causes of polycystic kidney disease (PKD) and TSC became evident, NIDDK's portfolio of research on PKD is increasingly relevant to TSC. NIAMS recently funded a study to identify the molecular basis of the finding that the loss of TSC2 promotes skin regeneration, which could have implications for addressing the skin abnormalities in people with TSC as well as restoring normal skin function for patients with severe wounds. Some people with TSC also develop lymphangioleiomyomatosis (LAM), a progressive, rare lung disease that almost exclusively affects young women. NHLBI supports research to investigate how TSC2 contributes to LAM at the cellular level. Based on this work, researchers are testing a combination therapy using two drugs that are already FDA-approved for clinical uses in a new mouse model that mimics features of human LAM.

To coordinate research efforts and facilitate communication among Institutes and Centers that support research related to TSC, NINDS continues to organize annual meetings of the Trans-NIH TSC Working Group with representatives from NINDS, NICHD, NHLBI, NIDDK, NCI, NIAMS, NIMH, The Office of Rare Diseases Research (a component of NCATS), the Department of Defense, and the TS Alliance (a nongovernmental TSC organization).

Item

Underrepresented Groups in Science. - The Committee commends OBSSR for its work to establish a comprehensive and cohesive process to track the efforts of government, universities, private foundations, and associations to enhance minority participation in the sciences. (p. 107)

Action taken or to be taken

The Office of Behavioral and Social Sciences Research (OBSSR) partnered with the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD), Office of Research on Women's Health (ORWH), National Institute on Minority Health and Health Disparities (NIMHD), National Institute on Drug Abuse (NIDA), National Science Foundation (NSF), and several non-federal organizations to sponsor *Enhancing Diversity in Science: Working Together to Develop Common Data, Measures, and Standards*. This workshop, held in May 2012, was organized by the Collaborative for Enhancing Diversity in Science (CEDS), a coalition of multiple professional organizations and scientific societies. The day-long event was designed to explore a more comprehensive and cohesive effort to track the many and various efforts of government, universities, private foundations, and associations to enhance minority participation in the sciences. It included discussion of the importance of diversity from the perspectives of leaders from NIH and NSF; the role of academic institutions in attracting and retaining diverse students and faculty/researchers; the role of professional organizations and scientific societies in gathering and tracking data; and the role of federal agencies in data collection. Additional panels included presentations from research and evaluation experts on developing and using metrics and the unique perspectives of racial/ethnic groups when gathering data across institutions. Breakout group discussions focused on metrics and processes for sharing best practices and research. The workshop report will be posted at [http://www.cossa.org/diversity/reports/Enhancing Diversity in Science Common Data Measures and Standards.pdf](http://www.cossa.org/diversity/reports/Enhancing_Diversity_in_Science_Common_Data_Measures_and_Standards.pdf), by the end of March 2013.

Efforts to track and improve minority participation in the scientific workforce are also a priority of the NIH Office of the Director. The special Working Group on Diversity in Biomedical Research Workforce (WGDBRW, <http://acd.od.nih.gov/dbr.htm>) of the Advisory Committee to the Director (ACD) was charged with providing concrete recommendations toward improving the recruitment and retention of underrepresented minorities, people with disabilities, and people from disadvantaged backgrounds across the lifespan of a biomedical research career from graduate study to acquisition of tenure in an academic position or the equivalent in a non-academic setting. The Working Group issued its report to the ACD on June 14, 2012. The report includes thirteen recommendations for the NIH Director to consider for increasing the diversity of the biomedical research workforce. These recommendations were based on the WGDBRW deliberations as well as consultation with stakeholders via a Request for Information and a public meeting. Several recommendations address the need for enhanced data collection and analysis, so as to better design and refine training and mentorship programs that produce optimal results. The WGDBRW collaborated and coordinated with the ACD Biomedical Workforce Working Group, the NIH Diversity Task Force, and the NIH Women in Biomedical Research Careers Working Group to develop the recommendations.